

TREATMENT IN GENERAL PRACTICE

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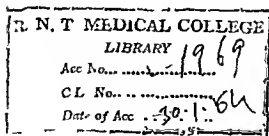
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PREFACE TO THE FOURTH EDITION

For a good many years we have been so superbly educating our young men that now we are reaping the whirlwind. Not all of them are any longer still "young," and as I continue in my effort to sort and test and organize the literature they are producing it becomes increasingly certain to me that a majority of them are imbued with a dissatisfaction the like of which no other period has ever known. The result is a great wealth of contributions, and since many of these are of undoubted value, the task of trying to weave them all into place in the tapestry of the whole has become very difficult indeed. I am aware of the inadequacy of my presentation in many places, but I have done the best that I could.

The following maladies are included for the first time in this present edition, some of them are little more than names for new sub varieties of diseases previously considered, but many are given full presentation as newly-included entities: *acute infectious hepatitis, acquired hemolytic anemia, alpha tocopherol (vitamin E) deficiency, Australian X disease, chromoblastomycosis, chronic infectious spondylitis, delayed menstruation, epidemic diarrhea of the newborn, epidemic encephalitis, equine encephalomyelitis, familial microcytic anemia, familial non hemolytic jaundice, Felly's syndrome, fibronitis, gas gangrene geriatrics, Haverhill fever, histoplasmosis, hyoscyamus poisoning, hypoprolthrombinemia (vitamin K deficiency), icterus gravis neonatorum, intermediary toxic hepatitis, intestinal influenza (epidemic vomiting and diarrhea), Japanese encephalitis, lumbago, Marie-Strumpell syndrome, Ménière's disease, muscular rheumatism, myositis, nicotinic acid deficiency, encephalopathy, premenstrual tension, pyridoxin (vitamin B₆) deficiency, Q fever, riboflavin deficiency, Russian encephalitis, St. Louis encephalitis, schistosoma dermatitis (swimmer's itch), sporadic encephalitis of unknown origin, Still's disease, strontium poisoning, sulfonamide toxicities and contraindications and combinations and antidotes, target cell anemia, torticollis, toxoplasmic encephalitis, toxoplasmosis, trench fever, tsutsugamushi fever, and von Bechterew's syndrome.*

Indebtedness is always a privilege and a pleasure to acknowledge. Jane Smith has helped with the reprint files, the added bibliography and the proof reading. Marie Chess has checked the earlier bibliography, and to her and to Robert Ota has fallen the difficult task of preparing the final typed copy from my longhand manuscript. The publishers have been splendidly cooperative as always.

HARRY BECKMAN

MILWAUKEE, WIS

PREFACE

THE neglect of thorough and painstaking teaching of therapeutics in this country is not so often the subject of *serious* consideration in our medical councils as it well might be. With only a few notable exceptions the medical schools seem content if there is presented within their halls, usually to Junior students who have had as yet practically no contact with the sick, a ridiculously inadequate course of lectures, the rest being left to the teachers in the departments of medicine, pediatrics, obstetrics, etc. And these latter seem to shift the responsibility largely onto the gods, not through any culpability upon their part, but simply because in their immersion in the task of acquainting the student with the prodigious methodology of modern diagnosis, no time is left for an exhaustive consideration with him of the treatment of disease. Hence it is that the therapeutic credo of the average young practitioner today contains but two articles: one, that there are certain therapeutic principles that invariably hold and that they need to be varied only in detail in the handling of particular diseases, and, the other, that the art of treatment is one that "comes" if only one has mastered the art of diagnosis.

It is in an attempt to shake, however feebly, the false foundations of these beliefs that the present book has been written. In it each of the principal diseases of man, exclusive of those that by prescriptive right belong within the domain of the legitimate specialties, has had its own peculiar therapy described, as that therapy has been evolved out of the experience of physicians all over the world. The true authors of the book, then, are those men and women whose names appear in the Bibliography. Whenever possible I have presented their work in their own words, but often it has been necessary to abstract and to condense, and not infrequently to present a subject in a manner and perhaps even from a point of view that has apparently little in common with that held by those who reported the original trials and observations. Always, however, I have looked upon myself merely as an editor, and I hope that no more than editorial liberties have been taken in any portion of the book. Of course it has not been possible to keep my own opinion invariably in the background, hence I elected in the beginning to write in the first person so that there might be at no time any confusion as to whose work or views were being presented.

Very humbly I recognize that the rather lengthy presentations of controversies that are to be found here and there in the book will give much offense to all save those who, like myself, have been even more disturbed by the indolent type of pedagogy that seeks sanctuary in the shameful words "Upon this point we can say very little as the authorities are at present in disagreement." Only as I have thought and taught through the years have I been able to write, a limitation which I suppose every author recognizes. As for the many other shortcomings of the book, I can only assure the reader that, no matter how grievous he finds them, they can in no wise affect him so deeply as they do me, for only I can know with what bright hopes the work was planned and begun several years ago.

To my wife I am deeply indebted for that intelligent and indefatigable assistance which is so invaluable in bringing a task of this sort to completion.

HARRY BECKMAN

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INFECTIOUS DISEASES

TREATMENT IN GENERAL PRACTICE

INFECTIOUS DISEASES

ANTHRAX

(Woolsorters Disease, Malignant Pustule)

Anthrax is an acute infectious disease of animals, especially herbivora caused by *Bacillus anthracis*. It is transmissible to man in whom it appears either in the cutaneous, pulmonary or gastro intestinal form. Workers in hide hair, bristles, wool, horn and bone are particularly susceptible, but it may be contracted by butchers, veterinarians, farm laborers and others in contact with animals. Pinkerton (1939) has reported a case contracted through pelting an infected mink. The disease is also occasionally contracted from an infected shaving brush. The incubation period is usually three to five days but may be as long as two weeks. The pustule and edema of the cutaneous form are usually of a distinctive character but there is often in the beginning considerable disproportion between these local changes and the amount of constitutional disturbance as evidenced by fever, rapid pulse and malaise. Consciousness to the end being characteristic, the appearance of delirium—indicating meningeal involvement—is always an ill omen. The symptoms of the pulmonary and gastro intestinal forms are not distinctive of the disease and thus the correct diagnosis is often made very late.

Anthrax was described by Hippocrates (460-370 B.C.) in one of the books of Epidemic Diseases thought to have been the authentic work of the Coan master, and it appears to have been well known during the period (732-1096 A.D.) of Arabian and Jewish ascendancy in medicine, but it is of interest to note that Galen (131-201 A.D.) had mistaken Hippocrates' description for that of erysipelas. The strange periodic malady of the middle ages *malum malannum*, may have been anthrax, which is known with certainty to have been epidemic in the early seventeenth century. I believe the first complete treatise on the disease was that of Cbabert in 1780. Koch demonstrated his cultures of the bacillus in 1876, the organism having been discovered by Davaine in 1850.

THERAPY

Local Treatment—Other than the application of warm boric acid compresses or of merely sterile gauze to collect the secretions, and the simple incision of an abscess if it forms, it is nowadays considered that nothing should be done locally except to put the part at rest. Koschucharoff (1938), who has had much experience with anthrax in Bulgaria, considers both incision and excision contraindicated, thermocautery, he states, may arrest the process if employed in the very early superficial stage but he marshals

many reasons against its routine employment. Most authorities agree that excision should not be done because of the difficulty of accurately defining the area to be excised and especially for the reason that general dissemination of the malady may be hastened by the manipulations. Enrich, discussing his treatment of 340 cases in the badly infected Bradford district in England, says that the results have been much better since the abandonment of excision in all cases except those in which the pustule is very small and on a site notoriously apt to favor rapid extension, such as the neck, but he insists that a limb should be fixed by splints and pillows or the head held in position by a towel carried across the forehead and fixed beneath sand bags. Lucchesi and Gildersleeve (1941) followed a strictly 'hands off' policy in their treatment of 67 patients without a fatality.

Technic of Excision (Dudley).—The skin is scrubbed gently with soap and rinsed thoroughly with sterile water, painted with aqueous 8 per cent, or stronger, phenol (carbolic acid) solution and rinsed with alcohol. Next the lesion is painted with collodion to avoid contamination of the incision. Eight per cent phenol is injected into the tissues all around the lesion to wall off the infective process. From 3 to 5 syringefuls of solution (about 60 cc.) will be sufficient. One-fourth inch outside of this phenolized zone, 5 or 6 syringefuls of 25 per cent alcohol are injected. These injections are usually made within $1\frac{1}{2}$ inches of the center of the lesion. The line of incision is painted with 8 per cent phenol, and an area from $2\frac{1}{2}$ to $3\frac{1}{2}$ inches in diameter is excised. After the excision, the base and edges of the wound are painted with pure phenol (95 per cent), which is immediately neutralized with absolute alcohol. The surface is cleansed with alcohol, and a wet dressing of boric acid, alcohol, or hypertonic saline solution, is applied. If this excision fails to stop the process free incisions are made into the tissues along the course of the edema and gauze drains are put in.

Antianthrax Serum.—The serum, made by immunizing horses against virulent anthrax organisms, has greatly reduced mortality throughout the world. It is given according to the dosage scheme devised by Regan (Table 1).

It will be seen that his systemic doses are all given intravenously, but some men of experience give the later injections intramuscularly. Gold (1935) has used larger than usual doses in his 10 reported cases—single doses of 400 to 500 cc. most frequently and in one case an initial injection of 1000 cc. Nine of the patients recovered; the average total dose in the recovered cases being 943 cc.

By 'local therapy' in Regan's scheme is meant the injection of 2 to 3 cc. at three or four equidistant points so as to circumscribe the lesion, the needle being inserted from 1 to $1\frac{1}{2}$ inches subcutaneously in the red indurated border just beyond the blanched zone. It is not generally agreed that the local injections are of value, and Gold was of the opinion that in the only one of his cases in which he used them they only served to spread the infection by the mechanical separation of the tissues which they effected.

Arsphenamines.—The drugs of this group have long been very successfully employed in South Africa, but only in recent years has their use begun in other parts of the world. Gilbert (1936) reports a series of 13 cases, 11 of the patients recovering when treated by neoarsphenamine alone. Only one intravenous injection of 9.6 Gm. was usually given, but if the edema persisted after twenty-four hours it was repeated. In all cases in which patients

TABLE 1—USE OF ANTHRAX SERUM

In absence of anthrax septicemia (as revealed by blood culture)			
	Intravenous dose	Number	Intervals
Mild cases with little constitutional symptoms, small lesion, no edema	50 cc	3 or 4	8 to 12 hours
	Subsequent injections at 12 to 24-hour intervals, usually not more than a total of 6		
	Local therapy every 12 to 24 hours		
Moderate cases with definite constitutional symptoms, medium lesion, moderate edema.	50 to 80 cc	3 or 4	8 hours
	Subsequently every 12 hours usually a total of 6 or 8		
	Local every 12 hours		
Severe cases with marked constitutional symptoms, large lesions, extensive edema	80 to 100 cc	3 or 4	6 to 8 hours
	Subsequently 50 cc every 12 hours		
	Local every 0 to 8 hours		
<hr/>			
In presence of anthrax septicemia.			
	100 to 150 cc		3 or 4 hours
	Continued to improvement or death		
	Local every 4 to 6 hours		

recovered the edema was relieved in thirty six hours and had disappeared in four days, the patients were ambulatory on the sixth day. Enrich (1933) is also impressed by the value of the arsenicals but he gives his two doses with an interval of one day between and usually combines the use of anti-anthrax serum with this newer treatment method. Gold used neoarsphenamine in addition to the serum in half of his 10 cases but was unable to note that it improved the patients' response in any way. Lucchesi and Gildersleeve (1941), summarizing their experience in 67 cases, felt neoarsphenamine to be the agent of choice unless the patient is afflicted with the internal type of anthrax, or the blood stream has been invaded, or the lesion is on the face or neck, in such instances they prefer to use serum. In Bulgaria, where from 800 to 1100 cases of anthrax occur annually, according to Koschucharoff serum is used almost exclusively, neoarsphenamine now being employed only occasionally.

Sulfonamides.—Bonnar (1940) has reported 2 cases in which sulfapyridine apparently saved life when serum and neoarsphenamine were failing. The animal studies of both Cruickshank (1939) and May and Buck (1939) indicate that something is to be expected of this drug, further clinical experiences will be awaited with much interest.

ASIATIC CHOLERA

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever, and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

BLACKWATER FEVER

I hesitate to commit myself on the delicate question of blackwater fever, indeed, I shall only state that there is a certain type of pernicious malaria (known as "hemoglobinuric fever") characterized by hemoglobinemia, hemoglobinuria, methemoglobinuria, 'methaemalbumin' in severe cases (Fairley and Bromfield, 1939), albuminuria, high fever and acidosis, vomiting, jaundice, anuria, rapidly progressive anemia and a high death rate—which some observers hold not to be malaria at all. However, there is strong evidence that *Plasmodium falciparum* is the causative organism in all cases though some observers hold that the syndrome may appear occasionally in benign tertian and exceptionally in quartan cases, and indeed the syndrome is said to have appeared in a few instances in individuals inoculated with these organisms for therapeutic purposes. Perhaps malaria with a tendency to blackwater has a different etiology from the ordinary form of the disease, and may be caused by a specific plasmodium—*P. tenue* Stephens as suggested by Sinton. Strickland and his collaborators believe that several varieties of mosquitoes may be grouped into the single species *A. funestus* which is capable of modifying the malarial parasites so as to make them more apt to provoke blackwater. Or the disease may be a plasmodium infection complicated by some other parasite, such as *Bartonella*, or by an unknown virus, or it may be evidence of sensitization to the proteo antigens of plasmodia, as suggested by Cernan Nunez. However, everything revealed in most of the careful studies of the occurrence of blackwater fever—such as the painstaking work of Whitmore in the West Indies and Central America, and of many others in Africa, India and elsewhere—supports the belief that the disease is a bizarre manifestation of malarious infection. But its distribution is not entirely the same as that of malaria for there are regions thoroughly saturated with the latter in which blackwater is not seen. Where prevalent it is usually the newcomers—and not always only 'white' newcomers—who are attacked, returned sojourners from malarious lands sometimes come down with it also even though they may not previously have had a typical malarial attack.

THERAPY

Quinine and Atabrine—Most writers do not favor the use of quinine believing that it is either the provocative factor or increases the severity of

the symptoms by increasing hemolysis. A large experience caused Brem, and Deeks and James, all of the Isthmian Canal Commission, to advise against its use during an attack. In Denderick's series of 2007 cases treated with quinine there was a mortality of 25.5 per cent, while in the 1188 cases treated without quinine there was a mortality of but 10.4 per cent. One must ever be on guard, however, against *post hoc ergo propter hoc* reasoning from statistical studies. Denderick does not hold that quinine should never be used, but states that the only conditions in which it is indicated are (1) where the parasites show no tendency to disappear after forty-eight hours from onset and (2) in the infrequent cases of intermittent hemoglobinuria where the outbreak corresponds with parasitic sporulation. Fairley and Murgatroyd (1940) report a case in which the capacity of quinine to produce blackwater fever appeared to be definitely related to persisting malarial infection, since after the apparent cure of the malaria quinine administration entirely failed to induce hemoglobinuria. Minson Bahr (1940), of the Hospital for Tropical Diseases in London, says that quinine in small doses may be used if atabrine is not available. Admitting that atabrine is to be preferred if any specific agent seems indicated at all, one should not overlook the fact, however, that hemoglobinuric fever of the blackwater type has apparently been caused by this drug also in a few instances.

Diuresis and Alkali Therapy—Suppression of urine, resulting apparently from the fact that the loss of fluid necessitated by the urinary elimination of free hemoglobin results in excessive concentration of the albuminous constituents of the blood, leads most physicians to attempt to get a great deal of fluid into the patient. Vomiting usually precluding the use of the oral route frequent small retention enemas of normal saline, or the introduction of saline by proctoclysis, is resorted to, or the saline may be given intravenously. The addition of 5 to 10 per cent of dextrose and 4 per cent of sodium bicarbonate will aid in sustaining the patient and combating acidosis. Hot fomentations to the kidney region are also helpful and analgesic as well.

Combating Anemia—There seems to be a good deal of fear that blood transfusion, which is so certainly indicated, may increase the hemolysis, but I do not see why this should be so if proper typing is to be had. In Southern Rhodesia, Blackie (1937) has given the subject careful study over a period of five years and concludes that transfusion is an important life saving measure if instituted early and repeated until there is evidence of active erythropoiesis, he believes that transfusions are contraindicated in toxic anuric cases.

The use of liver preparations, as in pernicious anemia (preferably of course by injection), is also rational. Iron and arsenic are useful later as in the convalescence following any destructive action on the erythrocytes, but the employment of neocarsphenamine for this or for its alleged specific action during the attacks has not met with favor among those most experienced in the handling of this disease.

Nursing Care—All agree that, because of the rapidly developing and severe anemia, there quickly arises great danger of circulatory failure of the type for which we unfortunately have no satisfactory remedial agents. The best weapon is prevention which takes the form not only of having the patient in bed but keeping him quietly there by allaying his apprehension and restlessness with sedatives (see *Insomnia*).

After-treatment—Blackwater fever nearly always terminates the malarial attack, but in the event of parasitic or symptomatic malarial relapse it is the consensus that a full treatment course with atabrine should be given

BRUCELLOSIS

(*Malta Fever, Mediterranean Fever, Undulant Fever*)

Brucellosis is an infectious disease caused by *Brucella melitensis*, *B. abortus*, and *B. suis*, the clinical manifestations being probably identical no matter which of these organisms is the infecting agent *B. melitensis* is harbored by goats, apparently without being harmful to these animals, and is contracted by the human being through direct contact with the animal or through ingestion of its milk. The disease is endemic and epidemic in the Mediterranean littoral and elsewhere in the world where raw milk from infected goats is consumed. Home (1933) contended, very interestingly, that it was unknown in Malta until British troops in 1856, enroute home during the Crimean War, brought it there from South Russia. Where prevalent, it is a difficult disease to stamp out for the reason that the goat is a profitable animal in these regions and the sterilization of its milk renders it decidedly objectionable in taste. Besides, the goat herders in the rural districts refuse to believe that such a disease exists, perhaps because of their own immunity owing to a gradual vaccination.

Owing to the increasing prevalence of the disease in the United States and other countries where goat's milk as the carrier could be practically ruled out, search for some other organism capable of causing the disease was rewarded by the discovery that *B. abortus* and *B. suis*, the organisms responsible for the infectious abortion of cattle, sheep and hogs, were also the etiologic agents in human brucellosis in many parts of the world. The disease, as contracted through ingestion of insufficiently pasteurized cow's milk, may of course appear endemically or in small epidemics, there are also many contact cases in farmers, butchers, sausage makers, and veterinarians, work with this organism in the laboratory is very dangerous. Transmission from man to man has not been demonstrated. It is generally considered that one attack of the disease confers lasting immunity, and immunization of those frequently exposed doubtless often takes place without the development of a recognizable attack.

The symptoms closely resemble those of typhoid fever with influenza engrafted upon it, i.e., there are more respiratory, myalgic and neuralgic symptoms than would be expected in typhoid, but tularemia, malaria and indeed a number of other acute infectious diseases need to be ruled out, for brucellosis is inclined to be protean in its manifestations. Rheumatic symptoms, orchitis and epididymitis are of frequent occurrence, middle ear disease, and pharyngeal and laryngeal complications resembling those of tuberculosis and syphilis, are seen, lymph gland involvement with a histologic picture like that in Hodgkin's disease, spondylitis, endocarditis, meningitis, meningomyelitis, encephalitis, osteomyelitis, intermittent hydrarthrosis, pleurisy

with effusion cholecystitis and focalized hepatitis hematopoietic damage, specific bronchopneumonic consolidation and numerous other symptoms or complications have been reported. In short in many instances the clinical diagnosis of acute brucellosis is made with extreme difficulty and now that the existence of a subclinical chronic form of the disease—taken out of the grab bag known as “neurasthenia”—is being increasingly recognized this disease has come to be one of major importance indeed. The usual incubation period is two weeks in the Mediterranean cases but it varies from slightly less than one week to several months here in the United States it is thought to be several weeks in most instances. The course even of the milder among the cases that are positively identified, is very protracted mortality is in general fairly low (3 per cent in the considerable experience of Huddleson *et al*, 1939 in the United States), but occasionally the attack may be of a quite malignant nature.

According to Calder *et al* (1939) the most striking feature of the blood picture in their 271 patients was active lymphocytosis with an unusually high proportion of immature lymphocytes in the peripheral blood coagulation time was also prolonged and clot retraction was imperfect. I think it is now the consensus that neither of the three tests—the intracutaneous, agglutination and opsonocytophagic—is of specific diagnostic value since any one of them may be positive in asymptomatic cases and all may be negative in cases proved by culture of the organism from the blood. Apparently these tests merely indicate, as does the tuberculin test in tuberculosis, that an infecting contact with brucella has occurred at some time, however, Calder (1939) is of the opinion—and I cannot say how many are in agreement with him—that if any two of the tests are positive the chances are about 70 to 1 that the clinical symptoms will be found compatible with a diagnosis of brucellosis.

THERAPY

The symptomatic treatment is such as would ordinarily be instituted in typhoid influenza, acute arthritis, etc. In addition a considerable number of other things is usually tried, and I have attempted to outline the method of employing the chief of these measures below. But it seems apparent that still today as in 1936, when Carpenter and Boak thoroughly reviewed the subject, we have no specific agent which can be counted upon to influence favorably all the cases in which it is used. Witness the report of Spink *et al* (1941) of 12 patients receiving only symptomatic therapy, 9 improved, of 11 receiving measures thought to be more or less specific, 7 improved.

Vaccine—It would seem that whatever is attainable with vaccine therapy is attributable to the general foreign protein reaction and is therefore obtained as easily with typhoid as with brucella vaccine, the latter is no longer Council accepted. Castaneda and Cardenas (1941), in Mexico, experimented with a vaccine prepared according to a new method but their results were not striking. It does not seem to me that the results obtained by Calder (1939) with a vaccine prepared by Foshay were very remarkable either, in some cases he thought intravenous administration of nicotinic acid was additionally helpful.

Hyperthermia—Prickman *et al* (1938), at the Mayo Clinic, treated a small group of patients by inducing fever in the Kettering hypertherm, they

felt their best results were obtained in acute and subacute cases. I understand this type of treatment is being employed currently with a modicum of success throughout the country.

Brucellin—Huddleson has been the chief advocate of a filtrate of a broth culture of brucella. If there is no marked systemic reaction in twenty-four hours to the preliminary intradermal injection of 0.1 cc. of this material (brucellin), he gives 0.2 cc. intradermally and 0.8 cc. intramuscularly in the afternoon or evening, this induces systemic reaction and he likes to induce such reactions three or four times at intervals of three days. Huddleson (1939) reports 500 cases treated by himself and a number of widely scattered physicians and considers the results favorable, but I am wondering if time will show this treatment to have more value than any other type of foreign protein therapy.

Whole Blood Transfusion—Quelvi and Nelson (1932) were very favorably impressed by their results with one or two transfusions by the usual method in 9 of their 10 cases, but since their report a good many transfusions have been given without setting any therapeutic rivers afire.

Immunotransfusion.—Creswell and Wallace (1936) reported favorably (see Index for method), but I have not seen a subsequent report of the use of this type of treatment.

Human "Immune" and Convalescent Serums—Poston and Smith (1936) injected human immune serum intraspinally in 2 meningitis cases, the dose of 16 cc. was repeated three times on alternate, once on successive, days. The serum was obtained from an individual who had been immunized eight years previously to several strains of brucella with no subsequent injections of vaccine. In 1938, Poston and Menefee gave 250 cc. of citrated blood intravenously from this same donor and thought the patient's rapid improvement was initiated by this treatment. Of course ordinary convalescent serum has been tried numerous times according to methods similar to those employed in measles and other diseases.

Antiserums—Goat antiserum, developed by Foshay and his associates, was reported upon by them (Wherry, O Neil and Foshay, 1935) as employed in 26 cases by widely scattered physicians. More recently, Flippin has used a bovine serum in 5 cases. These serums were thought to have been useful.

Chemotherapy—All the dyes have been employed intravenously, perhaps most frequently acriflavine (trypaflavine), Debono (1939), in Malta, thought this drug was effective in about 25 per cent of early cases, in doses of 10 to 15 cc. of 2 per cent solution every two or three days for 3 or 4 doses. Neosarsphenamine has been employed as in syphilis, and suadm as in bilharziasis, but the record of these agents is not brilliant. Abbott *et al.* (1937) used 10 cc. of the 1:1000 solution of metaphen intravenously in 10 cases, giving injections daily for a week and then biweekly when indicated, they thought the treatment worthwhile.

Latterly the sulfonamides have been on trial but their record is not as brilliant here as in some other diseases. To be sure, the early reports, usually of the result in only a single case, were all favorable, but more recently failures have begun to be reported, especially by those familiar with the fluctuating course of this disease. Bynum (1939) failed in 9 cases, Debono (1939) in 25 cases, Huddleson (1939) in 15 cases. I do not mean to imply that the record of the sulfonamides is upon the whole bad in brucellosis.

(indeed, Horn, 1940, reviewing 83 cases in the literature and adding 54 of his own, concludes that the chances of sulfanilamide favorably influencing the disease are two to one), but there is no begging the question that they have not been brilliantly successful. Best results seem to be obtained in early cases. At the time I write, the newer agents of this group have not yet been extensively employed in this disease. (The methods of using these drugs are discussed principally in the sections on Sepsis and Pneumonia.)

CEREBROSPINAL FEVER

(Epidemic Cerebrospinal Meningitis, Meningococcus Meningitis, Spotted Fever)

Cerebrospinal fever is an infectious disease which occurs sporadically or in epidemics and is caused by the meningococcus (*Neisseria intracellularis*), infection probably takes place by droplet transfer from an active case or from a healthy carrier. Symptomatically, and indeed perhaps pathologically, it can be divided into three stages, the first two of which are unfortunately not often recognized. The *first stage* may simply be a carrier stage without symptoms, or there may be a tonsillitis, pharyngitis, or sinusitis, or a conjunctivitis with discharge containing the causative organism. In the *second stage* the patient goes to bed, where he lies curled on his side, knees up and head bent toward them, he is extremely apathetic, loses both play of feature and modulation of voice, and when urged will complain in monosyllables of being "sore" all over his body. It is during this stage that the rash, which is usually petechial or purpuric, appears. In the *third stage* the diagnosis is most frequently made. Here there is the bursting headache, vomiting, chilliness and erratic fever, possibly delirium or coma (in children of course, often convulsions, and in infants a gastro intestinal disturbance or infection of the upper respiratory tract is often suggested), cloudiness of the spinal fluid, with increase in pressure unless block has occurred, stiff neck and the well-known Kernig's and other signs. The disease is characterized by what an irate friend of mine once called an "unnecessary" tendency toward complications, such as panophthalmitis, endocarditis and pericarditis, pneumonia, otitis media, purulent arthritis, internal hydrocephalus, etc. Relapses occur in perhaps one fourth of all cases, cases which run an entirely atypical course for several weeks are also not uncommon.

The greatest incidence of cerebrospinal fever is in children under ten, then in adolescents and then in young adults. Late winter and spring usually marks the peak of the seasonal increase in cases. Mortality varies greatly from year to year but prior to the use of sulfonamides in therapy it was always high—30 to 90 per cent or even higher. Nowadays it seems to be recognized that the condition known as Waterhouse-Friderichsen syndrome is simply acute fulminating meningococcemia with adrenal hemorrhages. During World War I cerebrospinal fever ranked sixth among the causes of death in U.S. Army camps.

So far as I am aware the first published accounts of cerebrospinal fever were those of Gaspard Vieusseux (1805) at Geneva, and L. Danielson and

E Mann (1806) in Massachusetts In 1811 the American Elisha North published a large monograph on the subject Weichselbaum discovered the causative organism in 1887, and Flexner introduced the antiserum in 1909

THErapy

Sulfonamides—The use of these drugs has completely altered the outlook in cerebrospinal fever in recent years Typical is the report of Banks (1940), who treated 80 consecutive patients of all ages with the loss of 5, a case mortality of 6.25 per cent Bryant and Fairman (1939), working under extremely primitive conditions in the Sudan, reported a mortality of 4.7 per cent in 189 cases in a fulminating epidemic In Great Britain in the winter of 1940-1941 there was the greatest epidemic ever recorded—but only from the standpoint of morbidity, for the mortality was kept down to about 5 per cent There is usually a return of the temperature to normal and practically complete disappearance of the other acute symptoms within two to six days—first signs of improvement are often seen within a few hours of beginning the medication delirium subsides or the eye of the comatose and apparently moribund patient loses its glaze, infants begin to feed again, the cerebrospinal fluid tends rapidly toward the normal (often becoming sterile within twenty-four hours), etc The incidence of complications and residual symptoms is also astonishingly reduced

Toxicity—See the chapter on Sulfonamide Toxicity at the end of the book

Choice of Sulfonamide—Sulfathiazole does not pass over into the cerebrospinal fluid very well and hence has not found a place in the therapy of cerebrospinal fever Both sulfanilamide and sulfapyridine do pass over, however, and both are effective Sulfapyridine has come to be preferred but is now likely to be replaced by sulfadiazine since Dingle *et al* (1941) have shown in 13 cases that sulfadiazine is fully as effective as sulfapyridine and considerably less toxic The methods of employing these two drugs are discussed in Pneumonia, the principal discussion of sulfanilamide is in Sepsis

Serum—It is now the consensus that the success of the sulfonamides in the therapy of cerebrospinal fever has completely outmoded the use of anti-meningococcus serum even as an adjuvant to chemotherapy Therefore a full and detailed description of serum methods will no longer be given, the following brief summary of the methods recently employed in the thorough study of Gregory, West and Stevens (1940) is merely intended as a guide to follow in the rare instances in which serum may still seem to be indicated (note these workers were comparing serum, antitoxin and sulfonamides and themselves became convinced of the superior value of chemotherapy) Alternate lumbar and cisternal injections of serum were made at intervals of twelve hours for the first thirty-six to forty-eight hours, thereafter once daily, preferably by the lumbar route, the doses were 5 to 10 cc less than the amount of fluid removed Immediately after the initial intraspinal injection and after a satisfactory sensitivity test for horse serum, a large dose of serum (30 to 60 cc for infants and young children, 90 to 120 cc for older children and adults), diluted two or three times with physiologic saline solution containing 5 or 10 per cent dextrose was given intravenously Ordinarily these intravenous injections were made only once or twice, but in very severe cases and in those with persistent septicemia, larger amounts were given several

times, preferably during the first twenty four hours. Intraspinal treatment was continued until two consecutive negative spinal cultures were obtained.

Hoyne (1940), who has had an enviable experience in the contagious disease hospitals of Chicago, opposes the intraspinal route, he has been giving all his serum intravenously for a number of years and in large dosage, 150 to 300 cc. He even feels that the success of sulfonamide therapy is attributable in part to the fact that no intraspinal treatment is given.

Differences in the locally prevailing strains of meningococci cause standard brands of serum to vary widely in their therapeutic value, if a patient does not respond as it is felt he should, a new supply of serum should be obtained from a different source.

Antitoxin—Like serum, antitoxin has been superseded by chemotherapy. Gregory *et al* (see above) used it in their comparative studies of alternate cases according to the same method and in the same dosages as employed with serum, the results were not as good as those with the serum. Hoyne uses larger doses (180 to 300 cc) and gives it all intravenously, he reports better results than most observers. According to Branham (1940) various lots of antitoxin are likely to differ in efficacy as do lots of serum.

Spinal Drainage—Frequent drainage of the spinal canal, without other treatment, was the sheet anchor of therapy prior to the development of specific measures and there are those who still champion it as adjuvant to other treatment, Thompson (1937), just before use of the sulfonamides began, even advocated a complicated type of continuous drainage. Bryant and Fairman say that the primitive natives whom they treated successfully with sulfonamides themselves noted the superior improvement in those who had also been tapped and soon demanded puncture in all cases. These workers feel that more than one puncture is seldom indicated. Hoyne goes so far as to say that one's aim should be to make as few punctures as possible. 'Frequent drainage is more apt to promote hydrocephalus than to prevent it. The fewer the punctures, the fewer the hospital days'—this opinion is based on a very large experience.

Other Measures—Morphine or dilaudid is usually given without stint to control violent symptoms during the first twenty four to forty-eight hours, though some observers believe they raise intracranial pressure and counsel against their use. Hoyne recently described the treatment of 134 patients, none of whom had been given any opiates.

Relapse—The entire cycle of treatment must be repeated with the same meticulous care used in the initial attack.

PROPHYLAXIS

The most practical measures for checking the spread of the disease when epidemic are isolation of the patient and disinfection of his clothing, bedding and discharges, the avoidance of crowds, fatigue and exposure and in barracks and camps, the spacing of individuals as far apart as possible. Drastic quarantining of whole areas or of infected healthy carriers was shown during the first World War to be impracticable.

Passive Immunization with Serum—It is believed by some that a single full therapeutic dose of antimeningococcic serum, given either subcutaneously or intramuscularly at the time of exposure, may have a protective action.

during three or four weeks, but accurate large scale study of the matter has never been made. Reactions depend upon the individual and the brand and age of the serum, the older the latter the less dangerous apparently. Of course it should be borne in mind that sensitization to horse serum may be the result of such injection. It seems to me that in view of the strain differences and the instability of the meningococcus there is reason to be completely skeptical of the value of this type of prophylactic measure.

Active Immunization with Toxin—Studies are under way by Kuhns (1938) and his associates in the U. S. Army, but their findings are as yet inconclusive so far as general applicability is concerned.

Active Immunization with Vaccines—Maclean and Bevan (1939) used a vaccine prepared from killed meningococci of a large number of strains during an epidemic on the island of Cyprus, but for insurmountable reasons they were unable to control the experiment satisfactorily and therefore, though they had some evidence of successful protection, they stated their belief that a convincing study of vaccination is yet to be performed.

Chemoprophylaxis—I have seen no report of the employment of the sulfonamides prophylactically but the attempt is certain to be made very soon during some epidemic threatening an Army encampment.

CHICKENPOX

(*Varicella*)

Chickenpox is an acute infectious and highly contagious disease of unknown etiology, which attacks nearly all children at some time during their early years. Several serious students are at present attempting to show a causal relationship between it and herpes zoster, but they have not yet succeeded. The malady is characterized by the sudden appearance of a vesicular rash usually without any prodromal or accompanying constitutional symptoms, when the latter do appear they are extremely mild. The rash may be differentiated from that of smallpox (a feat not always so easy of accomplishment as this glib statement would indicate!) by the fact that it begins on the back or some part of the trunk whence it spreads to the whole of the body, including the scalp but is seen on the face and palms and soles only occasionally and then to the extent of only a few lesions, that several stages of the eruption may be seen at one time, to wit, erythematous maculopapules, clear vesicles, turbid vesicles, somewhat pustular vesicles, and crusted vesicles and by the fact that these vesicles are unilocular (collapse completely after a single needle puncture) and are not umbilicated. Anomalous forms of the rash are occasionally seen. Johnson (1940) has reported a complete postmortem examination on an infant in which areas of focal degeneration showing similar pathologic changes as those demonstrable in the skin were found in the esophagus, pancreas, liver, renal pelvis, ureters, bladder and adrenal glands. In chickenpox there seems to be a strong stimulus to lymphocytic activity but, according to Holbrook (1941), a typical blood formula for the disease has not yet been described.

The incubation period varies from four to more than twenty days but most cases develop within twelve to fourteen days after exposure. One attack practically always protects for life, therefore, since most mothers are immune and transfer the immunity placentally, chickenpox in the newborn is rarely seen. So far as is known to me there is no racial immunity to chickenpox.

The disease was first described by Ingrassias (1553), but the most famous of the early treatises is that of Heberden (1767), which contains his original illustrations. Attention was first attracted to the possible relationship of chickenpox to herpes by Bokay in 1892.

THERAPY

Chickenpox is constitutionally a mild affair and usually requires no treatment. For control of the itching recourse may be had to the measures employed in smallpox. After scarring is very infrequent. Bullowa and Wislók (1935) tabulated complications in about 5 per cent of 2534 cases in hospital but the incidence is certainly lower in home treated cases. The most serious though very rare occurrences are doubtless massive skin gangrene and the form known as varicella pustulosa in which most of the poxles become furuncles or solitary abscesses. In these cases of course sepsis or bronchopneumonia is much to be feared. The lesions should be frequently cleansed with boric acid solution or perhaps it is preferable to immerse the patient for fifteen to thirty minutes several times daily in a warm bath containing a level teaspoonful of potassium permanganate to 4 gallons of water. The easiest way to prepare such a bath for the first time is to fill the tub to the desired point from a pail of known capacity. It is well to have the tub washed out afterward, to prevent permanent staining, with a solution of $\frac{1}{4}$ ounce of oxalic acid (poisonous!) to the quart of water, rinsing well afterward. Complications of the nervous system, such as encephalitis and encephalomyelitis, have been reported but are extremely rare and apparently always of good prognosis. Gangrene and extensive necrosis around the site of the poxles is a very serious but fortunately extremely rare complication.

PROPHYLAXIS

Vaccination—The vaccination of exposed individuals with the contents of chickenpox vesicles was introduced in Germany by Kling in 1913, but it has not been the consensus that it has much protective value, however, a favorable report (von Gulácsy, 1933) still appears now and then. The contents of a fresh vesicle, drawn up into a capillary tube, are introduced by the puncture or intracutaneous injection methods in all details precisely as in smallpox vaccination. The "take" occurs between the eighth and thirteenth days—papule, vesicle, crust, and possibly scar.

Convalescent Serum—The studies of Gordon and Meader (1929) indicated that the serum furnishes a high degree of protection if obtained within one month of the appearance of the donor's eruption, and that if obtained thereafter it is much less efficient. The blood is centrifuged, the serum from several donors pooled, passed through a Berkefeld filter and, after sterility tests over seven days, bottled in 15-cc vials. When stored in the ice-box the serum thus prepared is said not to lose its potency up to four months. The dose is 4 to 10 cc intramuscularly, severe reactions apparently do not occur.

Lewis Bareberg and Grossman (1937) failed to find such coalescent serum of the least value in protecting against the disease the results obtained by McGuinness Stokes and Mudd (1937) using hypodermic serum (pooled coalescent serum preserved by drying *in vacuo* from the frozen state and redissolved for use in about one-quarter its original volume of liquid), are inconclusive

COMMON COLD, GRIPPE, AND INFLUENZA

(*Catarrhal Fever*)

That the ordinary cold, grippe and epidemic influenza are different manifestations of one and the same thing may be debated profitably by bacteriologists and immunologists but from the standpoint of practical handling of these cases the point is not a controversial one. The successful treatment of all three is the successful prophylaxis of their complications. Existing epidemically as the common cold and grippe periodically and pandemically this disease appears as virulent influenza. Both the cold and grippe occur with greatest frequency during winter and spring. The virulent type of influenza shows no predilection for season when first it appears but always in the second and third waves which invariably characterize a pandemic there is a definite increase in incidence during the inclement months. The symptoms are almost too well known to warrant description here: typical cold in the head, headache, chilliness, pains all over the body, especially in the back and legs, impairment of taste and smell, a nonproductive cough with considerable soreness behind the sternum, fever, malaise, etc. The variability of these symptoms largely determines our diagnosis: if the attack is mild it is a cold; if severe and with the systemic symptoms predominating grippe; if the latter and occurring during an epidemic it is influenza.

Very interesting observations on the etiologic agent in this malady have been made in the years since Smith, Andrews and Laidlaw (1933) confirmed by Francis (1934) obtained a virus pathogenic for ferrets from the throat washings of influenza patients and demonstrated the production of antibodies against this virus during convalescence. The current etiologic nomenclature is the following: (a) clinical influenza cases from which the virus cannot be obtained; (b) influenza A cases clinically like the above but from which the virus of Smith *et al.* (there are many strains) can be obtained; and (c) influenza B cases clinically indistinguishable from the others but from which the new Lee virus described by Francis in 1940 can be obtained. Shope's (1939) recent work indicating that the virus of swine influenza which may be a prototype of the human disease spreads a portion of its life in the earthworm reveals an attractive new field for investigation. It is not thought that the influenza of horses is related to that of man.

Influenza derives its name from the fact that during medieval times when it was widely spread by the crusades it was looked upon as a cosmic or celestial influence (*influentia cœli*). Greenwood (1934) the eminent statistician is convinced that the English Sweats of the sixteenth century were outbreaks of this disease. The correlative occurrence of lethargic states

was definitely noted by Fernel at that time. Influenza was common in both the new and old worlds throughout the seventeenth and eighteenth centuries, in the latter century being dubbed *influenza* by the English and *grippe* by the French. The malady was more or less epidemic throughout the nineteenth century and pandemic in 1830-1833, 1836-1837, 1847-1848, 1889-1890. The visitation of 1918-1919, estimated to have involved 500,000,000 people and killed 15,000,000, is well known to many readers of this book. Webster (1939) has evolved a theory regarding the periodicity of influenzal outbreaks which if its value be established by further research, would be useful in predicting future epidemics and pandemics, however, it seems to me that according to his reasoning the epidemic in February, 1941, should have assumed greater proportions than it did.

PROPHYLAXIS

Chilling of any portion of the body and excessive fatigue both no doubt lower resistance to the infection and should therefore be avoided, especially during the inclement months. Jarvis (1939) believes that there is a type of individual whose respiratory tract does not adjust well to marked differences in temperature and that such persons should not sleep with the window open in severely cold weather. The crowding together of large numbers of people in closed spaces doubtless facilitates the spread of the disease, but whether prohibition of such meetings during an epidemic really affects the total morbidity is doubtful, since it would seem that a given epidemic of influenza persists until all who are not immune have become so or have died—bearing in mind that the new virus investigations are indicating the occurrence of a great many sub-clinical infections. Such prohibitions are justified however in that they doubtless delay the incidence in many cases until the virulence of the virus has been somewhat attenuated by a lessening of the rapidity of its passage through the human host. Further preventive measures may be dealt with briefly as follows:

Bacterial Vaccines—I am still unconvinced of the worth of either the orally or subcutaneously administered types. The studies of Hauser and Hauser (1939) at the University of Michigan, and of Diehl *et al* (1938-40) at the University of Minnesota, in both of which there were adequate experimental and control groups failed to demonstrate the practical value of these vaccines, the Council on Pharmacy and Chemistry of the American Medical Association has still not accepted them.

Virus Vaccines—There is as yet no convincing evidence (Horsfall, 1940) that the classical vaccine of this type has effectively prevented occurrence of the disease, but there is a new development which will be worth watching, namely, the observation of Horsfall and Lennette (1940) that in human volunteers a vaccine containing both 'influenza A' virus and canine distemper virus was very effective in raising the antibody titer against the influenza virus—at the present writing this still lacks the test of serviceability under epidemic conditions. Dalldorf *et al* (1941) reported an epidemic of "influenza A" among a hospital employee population of 826 adults half of whom had recently received the vaccine. The best they are able to say is that 'it may have reduced the incidence and favorably modified the severity of the disease'.

Masks and Sprays—The use of the gauze mask and the antiseptic or astringent nasal spray have yet to prove their cases in carefully controlled clinical experiments

Vitamins—Despite all the pother about it in the advertisements, there is not as yet any scientific evidence that excess of any of the vitamins—he it A or D or what have you—will prevent a cold, or grippe or ‘flu,’ or have any effect in curing it

Sulfonamides—There is not the least warrant for the use of these drugs in the attempt to prevent the occurrence of pneumonia, indeed one can only look upon such practice as definitely reprehensible in view of the toxic potentialities of these drugs

THERAPY

Symptomatic Treatment and Nursing Care—*Rest in Bed*—There are two chief indications, *viz.*, to keep the patient warm and to make him comfortable. The first of these can be met only by putting him to bed, and this applies as well for the common cold as for grippe or epidemic influenza. I think that all those who had extensive experience in the pandemic of 1918-1919, and were not seeking to show that some particular drug as used by them was marvelously efficacious, will agree that the occurrence of serious complications (which is the thing to be feared in this disease, since influenza itself is practically never fatal) was confined almost exclusively to those who either would not or could not go to bed at once on the appearance of symptoms. Though loath to overburden an already slogan weary world, my intense conviction on this point tempts me to advocate a facetious placard for display in all offices and factories: ‘Go home when you feel it!’ I believe the industrial world would suffer far less economically when next the disease is rife among us if the individual who insists upon tottering about as long as he can were subject to open scorn for his action. And the beam in our own eye? Who among us has not “stuck” at his post on the ward or in the clinic, or in the immensely more arduous pursuit of private practice, when he should really have been in bed with the ‘flu’? Surely to err here on the side of too much early care is to err not at all.

Relief of Discomfort—The patient, then, should be kept warm in bed, but whether it is necessary to carry this to the point of causing him to sweat is a moot point. The question was certainly answered in the affirmative in the beginning at least of the late pandemic, for salicylates and other diaphoretics were so generally employed by physicians that the lathy looked upon drenching sweats as one of the characteristic symptoms of the disease. One wonders how many patients were submitted to fatal chilling by this means. Many very competent clinicians deserted the excessive use of these drugs in treating the later waves of the disease. In the beginning, however, some such capsule as the following, to be repeated every three hours for only a few doses, will greatly relieve the patient’s discomfort.

R	Acetylsalicylic acid	gr	v	0 3
	Phenacetin	gr	iss	0 15
	Caffeine citrate	gr	ss	0 05

A ‘hot toddy’ of whiskey, sugar, and hot water is of value to many patients in the beginning, causing a mild diaphoresis, a considerable ameliora-

tion of the general bodily weariness, and a grateful lessening of apprehension. The old-fashioned Dover's powder (powder of ipecac and opium, U.S.P.) used very much to be employed for this purpose; the ordinary single dose (in capsule) of 5 grains (0.3 Gm.) Diehl (1933) found may be safely and well increased to as much as 15 grains (1 Gm.), but since he observed that powdered opium alone in equivalent dosage was equally valuable he concluded that the diaphoretic action of the ipecac was unimportant. Furthermore, out of his apparently well controlled study of the effects of opiates on the common cold emerged the fact that a combination of $\frac{1}{4}$ grain (0.015 Gm.) of eocodeine sulfate and $\frac{1}{4}$ grain of papaverine hydrochloride was more valuable than any other preparation in inducing prompt decrease or complete disappearance of the nasal discharge and congestion, and this without the unpleasant dryness that usually occurs when atropine is used for this purpose. Accompanying laryngitis, pharyngitis and tracheitis were not materially relieved. The following is his dosage scheme in terms of single capsules each containing the two drugs as above stated:

75 to 99 pounds:	1 after breakfast; 2 at bedtime
100 " 129 "	: 1 after breakfast; 3 at bedtime
130 " 169 "	: 1 after breakfast; 1 after lunch, 3 at bedtime
170 pounds and over:	1 after each meal and, depending on weight, 3 or 4 at bedtime

Unpleasant symptoms such as nausea, dizziness, headache and fainting were infrequent accompaniments of this medication; addiction to either of the drugs is not to be feared.

Another method of combating the excessive nasal secretion and relieving the feeling of fulness in the head is by the use of an oil spray, such as the following (though I must admit that the newer studies of lipid pneumonia have just about frightened me out of continuing to recommend this spray!)

R Thymol.	gr ss	0 03
Menthol.	gr iv	0 24
Eucalyptol.	gr x	0 60
Liquid petrolatum ...	ʒij	60 00

This will require the use of the oil nozzle on the atomizer, or, if preferred, 5 drops or so of the mixture may be placed well back in each nostril with the patient recumbent. Or a few drops of 10 per cent of menthol in alcohol may be inhaled from a handkerchief. A teaspoonful of the following inhalant may be vaporized by pouring scalding water upon it in a previously heated cup; with his head low over the cup, and a large towel enclosing both, the patient breathes with mouth open. Sometimes the feeling of stuffiness is only increased by such a steamy inhalant; exposure should be avoided for an hour after its use. The housewife will be grateful if forewarned that both the cup and spoon are very difficult to clean after their employment for this purpose.

R Oil of pine needles	ʒiv	15 0
Tincture of benzoin to make ..	ʒiv	120 0

If desired, creosote ($\frac{1}{2}$ drachm) may be added to the above, but as it is a mixture of phenols there is some reason to believe that if used too freely it may cause some damage to the kidneys. For bedridden patients, Means

and Lerman have found it convenient to place the above ingredients in an ordinary teakettleful of boiling water on a chair beside the bed a length of large rubber tubing is stuck onto the spout and the patient takes the free end into his mouth thus getting the full effect of the medicated steam without having to put his neck into an uncomfortable position

Nowadays the beadedrine inhaler is much employed for the relief of nasal congestion but some patients react unfavorably with restlessness and secondary reactions of the mucosa

For the relief of the substernal tightness and pain a mustard poultice is frequently employed This is conveniently made by spreading between two layers of thin muslin a paste made by mixing equal parts of ordinary household mustard and wheat flour stirred together with warm water it will not be nearly so effective if made with hot water Prepared plasters which are very convenient to use may be purchased at drug stores Whether the prepared or home made article is used it should be left in place over the upper part of the sternum until the skin becomes quite red which usually requires from fifteen to thirty minutes

Combating Cough—Relief of the tight cough will also lessen the chest discomfort but it should be remembered that therapy here must be in the direction of loosening and not drying the cough for experience shows that to dry up a cough or to lessen the patient's sensitiveness to it by repeated doses of an opiate is to invite the most feared complication namely pneumonia This is not to be taken to mean that opiates are never to be used on the contrary they are frequently of value but instead of using them in small doses routinely in conjunction with a cough mixture they should be withheld when possible until the patient shows signs of fatigue from the cough and restlessness and then a full dose may be given sufficient to ensure several hours of satisfying strength renewing rest Among the expectorants ammonium chloride is probably the most certain in its action (but *not* if used as enteric coated tablets) Some such preparation as the following which contains approximately 8 grains of the drug to each teaspoonful is usually effective if given every two hours

R ^x Ammonium chloride	3v	15 0
Syrup of citric acid	3j	30 0
Water to make	3iv	120 0

Frequently the drug is used as in the following prescription in which the brown mixture—containing too little of its active ingredients (paregoric tartar emetic and spirits of aromatic ether) to be usually effective alone—very satisfactorily supplements the action when used as a vehicle

R ^x Ammonium chloride	3iv	15 0
Compound mixture of glycyrrhiza to make	3iv	120 0
Label 1 teaspoonful every two to three hours		

A sip of pineapple juice after ammonium chloride very nicely overcomes the taste If the drug nauseates sodium citrate may be substituted in 10 to 15 grain doses it has the added advantages that it is a diuretic and indirectly an alkali Or 2 or 3 drops of a saturated solution of sodium or potassium iodide may be given in water every two hours but bearing in mind the frequent occurrence of iodism the interval between doses should

be lengthened as soon as possible. The syrup of hydriodic acid is well taken by children in doses scaled down from 1 drachm according to size and age. However, bronchial irritation may be aggravated by the iodides. Syrup of ipecac is frequently used also. The U.S.P. expectorant dose is 12 minims, but this is too large if the drug is to be repeated often, which is the only way to get results with it. Therefore the best dosage is 5 to 8 minims every two hours, for thus nausea is unlikely to occur.

R	Syrup of ipecac.....	5iv	15.0
	Aqueous elixir of glycyrrhiza to make	5iv	120.0
	Label: 1 teaspoonful every two hours.		

For a child, with its preference for sweets, the syrup of glycyrrhiza had best be substituted, or any of the other vehicles liked by children may be used—syrup of raspberry, syrup of tolu balsam (vanilla-like flavor), syrup of cacao (chocolate flavor), syrup of cinnamon. Evidently the profession, at least in England, is very fond of the use of iodides and ipecac in cough, for when Alstead (1939) questioned their value he was very tartly reprimanded in a letter "to the editor" of the *Lancet*.

When it is felt that a full effective amount of an opiate should be incorporated in the cough mixture, some such prescriptions as the following may be written (the doses are for adults, of course):

R	Pantopon.	gr iss	0 10
	Syrup of cacao to make	5iv	120 00
	Label: 1 teaspoonful every three hours		

The pantopon is present here in 1/20-grain doses. Dilaudid in the amount of $\frac{1}{4}$ grain (0.03 Gm.) could be substituted for pantopon; the teaspoonful dose would contain about 1/64 grain.

The following are satisfactory codeine prescriptions.

R	Codeine phosphate	gr. vuss	0 45
	Ammonium chloride	5iv	15 00
	Syrup of citric acid	5j	50 00
	Water to make.	5iv	120 00
	Label: 1 teaspoonful every three to four hours		

R	Codeine phosphate	gr. iv	0 24
	Elixir of terpin hydrate to make.	5iv	120 00
	Label: 1 teaspoonful every three to four hours.		

The first of these prescriptions contains approximately $\frac{1}{4}$ grain (0.015 Gm.) of codeine phosphate, the other $\frac{1}{2}$ grain (0.01 Gm.) per dose; it is well to bear in mind that elixir of terpin hydrate contains about as much alcohol as does whiskey. A larger amount of codeine may be needed, though Davenport (1938) has found that in most instances in tuberculosis sanatorium practice the smaller doses suffice. (Interestingly, he raises the question of codeine addiction and indicates that closer study might disclose that it is a matter of some moment; I imagine it would be very difficult to sustain this thesis.)

Cathartics—And now the question of the initial cathartic. I well remember my late professor of medicine as, with serious mien, he said to us many a time in class, "Gentlemen, I *always* prescribe calomel on the first visit," and

then, with a sly twinkle in his eyes, "or on the second" And doubtless he did just that But why? Certainly if a cathartic is to be used at all it had best be calomel, or at least not a saline, for Macht and Finesilver have conclusively shown in both laboratory and clinic that the taking of a saline cathartic prevents the absorption, and therefore the effect, of other drugs taken simultaneously or quite some time later But why give a cathartic at all when we know the debilitating effect of a purge even in a well individual? Some time ago the following facetious letter, which has caused me much amusement, appeared in the Journal of the American Medical Association, I quote almost *in toto*

*"To the Editor—*I appeal to the fountainhead of medical knowledge for information on a subject of greatest personal and community importance Shall I take a physic? And shall I give a physic to practically all my patients? I have not taken a physic for nearly fifteen years and am in perfect health My intestinal exit operates as faithfully as the inlet with an almost unvarying ratio of three to one Traffic occasionally slows up a bit and as a consequence terminal unloading facilities may be put to some test, but this is never extreme and there have been no failures nor needed repairs Once in a long time I have a cold but in no instance has a cold ever slowed up deliveries Years ago I always took a physic for my colds which always did two ugly things to me They always gave me a bellysche and disturbed my regular evacuating habits My colds without physies are just as brief as those subjected to the foregoing complications

'Now as to my patients They all want a thorough cleaning out and 'a change in diet' Regarding diet I am frequently distressed with my inability to supply new formulas and combinations but I am not now asking for any relief in this particular However, I do want enlightenment on the contention that if the patient suddenly shows a little fever or a subnormal temperature or restlessness or tympanites or a collapsed abdomen or frequency of bowel movements or a total atonement or numbness of the first three fingers on the right side, or anorexia, or a glutinous appetite or nausea with or without vomiting or a sudden dislike for the male parent, that such a patient should at once have a physic And if so what? and when? and how long?

"A new treatise on skin disease just came to my notice and in going through it in a quick review my memory may not serve me perfectly but I can now recall just one condition that did not require a purge a physic or a complete overhauling of the eliminating machinery, and that was freckles I was pleased as I have freckles and it may be safe to go right on neglecting my bowels as heretofore with safety I have no more trouble keeping my bowels regular than my nose Roman, and I have about come to the conclusion that colds or no colds, I need plastics for my nose just as frequently as physies for my bowels and that's that

"Such limited reading of last editions as I do gives me scant support for my aversion to purges and thorough cleaning out of the intestinal tract' My frequent contact with physicians convinces me that I do far less cleaning out than they do and when it comes to toning up a liver with laxatives I am almost a total failure I try In this community one simply must be able to do considerable in the way of toning up livers. It seems that we live in the tanelless liver belt and since Marshall Field established that the customer is always right we must tone 'em up as per general request or they will get another toner I do not know whether the people or the physicians established this belt but it's here all right and we live in the center of it At a recent meeting of our society I informed my confrères that I was making no effort to transform my cold cases into dysentery cases and now I wish I had not for I fear I lost caste or something

E O HARROLD M D

Well, well! But this matter should be put to the test Macdonald made the attempt and, though his series was small and not subject to very rigid control, he showed that during an epidemic of mild catarrhal fever occurring in an industrial plant, the loss of time among those who had taken an initial cathartic was 14.3 per cent greater than among those not so dosing themselves In Glazer's (1930) small series of cases cathartic dosing did not seem to affect the course one way or the other Smith and Baier (1939) felt that castor oil and magnesium sulfate as employed by them in 520 cases with

493 controls (all patients having temperatures ranging between 100° and 102° F) actually prolonged the attack. This last study was performed at Fort Benning, Ga., and is indicative of the type of study which should soon become increasingly feasible with our large numbers of conscripts.

Fluid Allowance—As in all other fevers, water should be liberally given. The patient should take at least $\frac{1}{2}$ tumblerful every hour while awake. It is often easier to induce the taking of this much fluid if it is given in the form of lemon- or orangeade. This fruit juice, since it is potentially alkaline, also helps to meet what is generally looked upon as a definite indication, namely, the necessity to overcome acidosis. Whether this acidosis actually exists or whether the effectiveness of "alkalinizing the patient" is only an unfounded clinical tradition, is not definitely answered so far as I am aware. Ten to 15 grains of sodium bicarbonate added to the glass of lemonade will help in accomplishing this desired result. In those cases in which there is nausea and vomiting, fluids should be given by rectum. From 2 to 8 ounces, according to the patient's size, of a 2 per cent sodium bicarbonate solution may be given as a retention enema every two to four hours until the stomach will retain water.

In leaving this subject of fluid allowance, perhaps it should be pointed out that there is a rather large group of physicians, apparently quite orthodox fellows in all other respects, who doubt the advisability of making the patient fairly swim in water unless he has shown some previous evidence of being in a state of dehydration, however, since Harrold (1936) has pointed out that no one ever heard a fish soeze, the practice of "pushing fluids" probably has a rational basis.

Diet—In the beginning, when the patient is feverish and feeling quite ill, he will likely be uninterested in taking more than the fruit juice referred to above; if this is fairly well sweetened he is of course getting a bit of nourishment. Ideally, if the siege threatens to last a number of days, it would be well to have him drink a quart of milk (reinforced by about a half pint of cream if he will accept so much "richness") during the twenty-four hours and offer him a couple of soft-cooked eggs and a small portion of cooked cereal at one or other of the usual mealtimes. See Index for an eggnog recipe. Later, in leading back to full diet, reduce the milk and add small amounts of bread and butter, lean cooked meat, and a bit of green vegetables or huttered baked potato if the aroma of that will tempt him. Occasionally a patient with grippe will develop a quite voracious appetite after a few days, in a circumstance which we often meet by denying him all he wants because he is "lying inactively in bed," but Davis' (1934) studies indicate that perhaps in infants and young children at least our counsel of abstemiousness may not be so wise. In her work in a nursery in which, regardless of the height of fever, the youngsters were allowed to continue the choice of their foods during the course of colds and tonsillitis, she not only confirmed the well-known fact that appetite decreases twenty-four hours before there are any other signs of illness, but also observed that twelve to twenty-four hours before the fall in temperature or improvement in signs there was a sharp increase in desire for food. A child with high fever and several days' lack of interest in his food would suddenly sit up when his tray came in and eat heartily, with second and third helpings, of meat, potatoes, and vegetables, no digestive disturbances resulted and convalescence followed predictably.

the next day. It is interesting also that regardless of their predilections when well, these children turned with enjoyment to raw beef, beets, and usually carrots when recovering from acute upper respiratory infections.

Other Measures—These are legion, and so diverse have been the offerings of drugs having specific value both in the United States and other countries that I believe none of them merit description. The sulfonamides have made no place for themselves here when administered systemically, perhaps one should note, however, that the saturated solution of sulfanilamide in water has recently been advocated for use as a spray.

PNEUMONIA AS A COMPLICATION

This is of course the thing chiefly to be feared, particularly the type of bronchopneumonia which prevailed during the pandemic of 1918-19. The treatment of pneumonia is separately considered elsewhere in this section on the Infectious Diseases.

CIRCULATORY COMPLICATIONS

There is wide divergence of opinion among competent observers regarding the frequency and type of cardiac involvement in cases not complicated by pneumonia, but in comparison with acute rheumatic fever, cerebrospinal fever, and diphtheria the occurrence is certainly rare. Hamburger (1938), of the Michael Reese Hospital, Chicago, reviewing his own experience with that of others, lists various arrhythmias, dyspnea, palpitation, anginoid pain, extreme malaise and exhaustion, he even cautiously ventures the opinion that disorders of the conduction pathways of the heart are pathognomonic of influenza as is mitral stenosis of rheumatic heart disease. The treatment of these things is considered in the section on Circulatory Disturbances.

As for peripheral circulatory failure (shock) there is little to say save that it was of frequent occurrence during the 1918-19 outbreak and that what little there is to do in the circumstances is discussed in the chapter on Pneumonia.

ACUTE PARANASAL SINUS INVOLVEMENT

The anterior group of sinuses—the frontal, the anterior ethmoidal, and the maxillary antrum—open into the middle meatus beneath the middle turbinate, the posterior group—posterior ethmoidal and sphenoidal—open far back and high up above the middle turbinate. While the former are more often involved than the latter, it would seem advisable for the general practitioner to consider all the sinuses equally affected in any given case for he can hardly show preference to one or the other in the application of his nonspecialized therapy and he will nearly always be actually justified in his assumption since infection in cavities above or below the ones suspected of being principally involved is doubtless an important factor in preventing quick recovery in the majority of instances. Bearing in mind that most patients recover spontaneously in one to three weeks except when the attack occurs during an influenza epidemic of some virulence treatment should have simply the following objectives: to clear the passages, reduce congestion, attack the causative organisms if this is feasible, and resort to surgery only when imperatively necessary.

Clearing the Nasal Passages—Hawking back into the nasopharynx and then expectorating the accumulations is less dangerous than nose blowing but of course young children cannot perform this act. Some of the exudate can be got out through the nostrils by medicine dropper suction. One should proceed very cautiously and gently in the application of more forceful mechanical methods than this if secondary engorgement is to be avoided. If the nose must be blown it should be done with both nostrils wide open. Parkinson (1935) well emphasizes the fact that the familiar method of blowing while the nostrils are partially closed with the fingers or while one is completely occluded with the other wide open can force secretions back into the sinuses or nut into the eustachian tubes. In any case blow gently!

For best drainage it is probably advisable to have the patient at least partially upright with the head comfortably supported in a position of slightly forward flexion. Layton (1935) makes the point that too great flexion however is likely to increase the headache. He feels that unless otherwise too ill the patient does better in an armchair than in bed. Keeping the room warm and the moisture as high as possible are helpful measures. The use of a steamy inhalant (see *Relief of Discomfort* in this present article) is also indicated but in view of the findings discussed below (under *Sprays and Drops*) it may be advisable to employ merely steam alone without the addition of any medicinal ingredients.

Among conditions favoring obstruction to drainage and thus potential prolongation of the siege are deflected septum, hypertrophied turbinates and nasal polypi. Howarth (1935) feels that a careful rhinological examination—presumably by a specialist—is a necessary preliminary to any forecast of the duration of the condition but unfortunately removal of these obstructions does not by any means always effect amelioration. Similarly there is disagreement among rhinologists regarding the advisability of routinely removing simply hypertrophied tonsils and adenoids in these cases though the consensus seems to be that if septic they should come out.

Reducing Congestion—It is probable that the most important aim of treatment is to facilitate drainage from the sinuses by reducing congestion of the mucous membranes about the openings into the meatus and it is just this thing which we are not often able to accomplish satisfactorily. Not that the mucosa cannot be shrunk—nothing is easier really—but to do it without causing a reaction of turgescence or greatly slowing or stopping entirely the movement of the cilia of these membranes there lies the difficulty. Investigation of the cilia which sweep all secretions back toward the esophagus has disclosed that any measures which retard their movement are apt to postpone the patient's recovery from an acute attack or convert the condition into a case of chronic sinusitis. The following measures are discussed with this in mind.

Sprays and Drops—The investigations of a number of workers since 1933 (see Lierle and Moore, Proetz, McMahon, Fenton and Larsell, Walsh and Cannon and Cannon in Bibliography) have indicated a number of surprising things with regard to heretofore commonly employed drugs. In brief the observations are as follows: (a) Physiologic solution of sodium chloride has no effect on either cilia or epithelium. (b) Both tap and distilled water promptly stop ciliary activity and liquid petrolatum (albolene) markedly slows it. (c) From 0.5 to 3 per cent of ephedrine in physiologic solution of

sodium chloride does not affect the cilia (d) Epinephrine (adrenalin) 1 5000 to 1 1000 in normal saline slows or paralyzes and so does cocaine in more than 2.5 per cent strength (e) Mild silver proteins of the type of argyrol and neosilol are incompatible with the salt solution and when used in water definitely slow the ciliary activity Ten per cent concentration of these drugs in contact for twenty minutes with the mucosa of the frontal sinuses of the dog caused edema and intense cellular concentration throughout the mucosa and actual fragmentation of the columnar epithelium (f) Eucalyptol, menthol, thymol, zinc sulfate, mercurchrome, and merthiolate all cause slowing or paralysis of ciliary activity depending upon their concentration (g) Only vehicles are dangerous from the standpoint of liability to induce lipoid pneumonia, and some much used agents such for example as the mild silver proteins, are also prone to cause comparable pulmonary tissue reactions

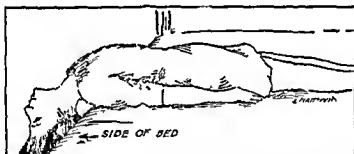
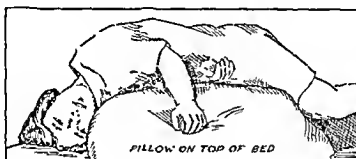
Therefore, of the astringents principally used—cocaine, epinephrine (adrenalin), zinc sulfate, and ephedrine—only the latter would seem to be advisable from the standpoint of effective shrinking of the membrane without harmful action The following prescription, useful as either spray or drops contains 1 per cent of the active drug in 0.9 per cent saline, it may be sterilized by boiling and will then keep for many months without the addition of a preservative

R	Ephedrine sulfate	gr xx	1 2
	Sodium chloride	gr xviij	1 0
	Water to make	℥iv	120 0
Label Use as nose spray or drops as directed			

Parkinson (1936-39) strongly advocates the "lateral head low posture" in introducing drops into the nose Reference to the diagrammatic sketch will show how this position differs from the common one in which the patient lying across the bed drops the head back against the bed's side in order to approximate the upside down position, a young child must be forcibly held thus and to propose putting him into the position a second time "is notice to start a riot," as Reese (1934) well says The lateral head low posture is less formidable and more nearly comfortable Parkinson sprays the nose at intervals of several minutes with the ephedrine solution in order to accomplish as thorough ventilation as possible, then, the patient placed in the lateral posture, at least one dropperful of the solution is instilled into each nostril, the position being held for three to five minutes during which time mouth breathing prevents the fluid from being drawn into the pharynx Finally the head is rotated to face downward and the patient remains thus for a few more minutes to allow the fluid contents to be expelled from the nose These treatments can be repeated several times daily with spraying in the interim

Everyone admits, I think, that ephedrine will vigorously contract the arterioles and produce a period of ischemia and shrinkage of the membrane which is ideal for drainage, but many men have given up the use of the drug because of the stinging sensation in the beginning and the subsequent reaction of engorgement, these things, however, are said not to occur if the drug is applied in physiologic saline solution as in the prescription above Benzedrine, in the well known inhaler, may be used satisfactorily by some

patients but others are made very restless by the drug and suffer from sleeplessness throughout the night if they have sniffed at any time during the evening. Peters and Faulkner (1930) studied the effects upon the pulse, blood pressure, and electrocardiogram, as well as the subjective symptoms, of 57 patients with various types of cardiovascular disease; each patient took five deep inhalations into each nostril in the course of two minutes. Their conclusion was that neither heart disease nor hypertension *per se* contraindicates the use of the benzedrine inhaler but that it should be used cautiously if at all in patients with angina pectoris since in occasional cases it may precipitate an attack. I would point out that their findings indicate nothing with regard to frequent inhalation over a long period.



A prescription for drops, much used by rhinologists (Reese), is the following.

R	Cocaine (alkaloid)	gr. 1	0 06
	Camphor...		gr. 1	0 06
	Oil of cinnamon ..		℥j	0 06
	Liquid petrolatum to make		℥j	30 00
Label: Drop into nose as directed.				

The amount of cocaine here (less than 0.25) is not sufficient to check ciliary action but enough to cause some slight shrinking, and its presence prevents refilling of the prescription without permission. But the oils have adverse action on the cilia (see above), and Walsh and Cannon (1938) point out that they may quickly make their way into the lungs and there set up a lipoid pneumonia; one wonders if merely the cocaine in normal saline might not be just as effective without having any deterrent action—a prescription such as the following:

R Cocaine (alkaloid)	gr j	0 06
Sodium chloride	gr ixxx	0 27
Water to make	℥j	30 00
Label Drop into nose as directed		

The introduction of cotton tipped applicators or tampons soaked in stronger cocaine solutions seems inadvisable in the present state of our knowledge, at least the general practitioner may well talk himself past this point for if the patient gets on nicely without these ministrations he is likely to overlook their omission, while if he must ultimately be referred to one of the gentlemen who specialize in the treatment of these cases in the chronic stages one may be sure that he will thenceforward be probed to repletion.

Attacking the Causative Organisms—Even though the older antiseptics had not been shown to be detrimental to ciliary action there would be no true rationale in their use here for the reason that sterilization of no mucous membrane can be accomplished by such local applications. They give rise to an undesirable secondary reaction also, which Reese has well dubbed "mucosal diarrhea." And furthermore, argyrol dropping has long been traditional in most families, when the doctor is finally called he is expected to know several tricks far superior to that. The newest fad is of course to use a spray of 5 per cent sodium sulfathiazole, but I have seen no published proof of the efficacy of this measure. So far as I know the effect of such a spray on the nasal cilia has not been studied, irritation and even necrosis of tissues has been reported, however. If such solution is to be used only a two days' supply should be prescribed for the reason that decomposition occurs rapidly and the decomposed is even more irritant than the fresh solution.

I do not believe that the value of any vaccines, be they orthodox or the new undenatured bacterial antigens has been shown as yet.

If the patient is suffering from any one of the vitamin deficiencies his resistance will be of course immensely improved if the missing factors are supplied but we have no proof or even strongly suggestive evidence that the feeding of any of the vitamins in greater abundance than provided in the ordinary well balanced diet is of the least value in promoting recovery. Likewise the malnourished individual requires building up but there are no magic essences whose administration will promote the equivalent of this slow process in shorter order.

The dry climate of inland mountainous regions is beneficial to some patients, others profit by a long ocean voyage or sojourning for a while on a warm seacoast.

The sulfonamides administered internally are of course being tried but the success attained so far has only been moderate. It is said that the occurrence of a positive blood culture in acute sinusitis is extremely rare except as an indication of invasion of the stream from some other focus.

Surgery—When, despite treatment such as outlined in the preceding pages, the pain and headache increase, temperature rises, and the surrounding tissues begin to swell, it is felt by many that resort to surgery should be had, at least otorhinologic consultation at this time may be to the advantage of the patient.

OTITIS MEDIA AND COMPLICATIONS (*Mastoiditis and Chronic Suppuration*)

When infection spreads into the eustachian tube this passageway quickly becomes occluded by the swelling of its mucosa and products of inflammation accumulate thereafter in the infected atrium or lower cavity of the middle ear. In most instances it seems that the curtains of swollen mucous membrane which separate the attic with its contained ossicles from this lower space are not easily penetrated, so that rupture and escape through the less resistant ear drum take place if the inflammatory process continues for long or if pus accumulates quickly in large amount.

Early Treatment.—In the beginning relief of pain is indicated while waiting for the severity of the involvement to become manifest. Opiates seriously mask the symptoms and should not be used, but ear drops such as the following are much employed:

R	Phenol	gr xiv	1 5
	Glycerin	3j	30 0
Label. Warm and introduce 3 to 5 drops in ear every 2 or 3 hours			

Hot applications, either in the form of the electric pad, hot-water bottle or poultices will also bring much relief and aid in "pointing" the process. The linseed poultice (see Index) retains heat a long time but its weight on the ear is sometimes objectionable.

Incision (Paracentesis).—As pressure of the pus increases so does the pain and in young children fever often rises quite high; adults may remain afebrile but will complain of noises in the head and deafness on the affected side. The landmarks disappear from the ear drum, the light reflex is lost, and the drum becomes dark red and begins to bulge. Now arises the question, should incision be made at once? I know that the almost unanimous "yes" of the rhinologists seems to supply a very definite affirmative answer, but perhaps the point is a bit finer than this. Is it not true that the cases which rupture spontaneously usually do so before the practitioner has had much time to ponder the question to cut or not to cut, and that the frequent necessity to add an incision even after the rupture indicates a quite fulminant quality in these infections? Of course the query cannot be answered because "incise when it bulges" is so much the rule nowadays (even a normal infant's drum may bulge when it cries, you know) that opportunity is rarely given the slowly developing cases to subside as slowly again without benefit of surgery.

Local Anesthesia.—Curry (1936) of the Cook County Hospital describes the procedures as follows: "Equal parts of phenol, menthol, and cocaine hydrochloride are used. This thin paste is applied sparingly with a small cotton applicator to the bulging area of the ear drum. It is well to warn the patient that the first touch hurts. The swab is held in place as long as the patient can bear it, which is usually a few seconds. The same procedure is continued until the applicator can contact the inflamed ear drum without much discomfort for a minute or two. The incision is then made through the bulging area of the ear drum, which should appear white if properly anesthetized, with a light paracentesis knife. If there is no bulging, the incision is made in the posterior quadrant of the ear drum. In certain types of influenza

ears, the drum cannot be seen because of blebs. These can be opened only by guess. With gentleness and care, an experienced surgeon can insert the knife through the blebs and toward the ear drum until the point of the knife gently strikes the promontory without harm. I have found no need for extensive incision of the ear drum. If the tympanum continues to fill with pus, the small incision enlarges with the infection. If drainage is slight, the small or large incision closes quickly and another opening may be required."

General Anesthesia—Ethyl chloride sprayed on an open-mask over the nose and mouth is satisfactory for one experienced with this useful anesthetic; or vinyl ether (vinethene) may be used by the drop method. Of course nitrous oxide or ethylene is ideal but expensive and often unobtainable for a patient quarantined by the primary infection.

Treatment after Incision.—With the establishment of free drainage pain disappears and subsidence and resolution of the process occur fairly rapidly in most cases. The objects of treatment at this time are to facilitate evacuation of the seropurulent discharges from the middle ear, promote their removal from the external auditory canal and prevent irritation of the external ear. Rhinologists are divided in their allegiance to wet or dry methods of accomplishing these things, so I shall describe them both.

Wet Treatment—Immediately after operation or rupture a gauze wick is carried in as far as the opening in the drum and replaced frequently during about forty-eight hours. Then irrigation is instituted with the following approximately saturated solution of boric acid as hot as can be borne (about 110° F); the soda aids in dislodging a sticky discharge but may be omitted.

R) Boric acid 3x	40.00
Sodium bicarbonate	. 3x	40.00
Water to make . . .	Oj	1000.00
Label: Use for irrigation of ear		

The irrigations should be performed gently with the ear held downward over a pan and repeated three or four times daily. Between treatments a wick may be kept in the canal or the phenol-glycerin drops (see above) may be diluted with an equal quantity of boiled water and instilled. Some men prefer to swab the canal dry after the irrigation while others do nothing; a gauze pad may be applied over the external ear and conveniently held in place by a hair net tied under the chin.

If blockage takes place as indicated by return of the earache, a few drops of hydrogen peroxide are instilled to reestablish drainage.

Dry Treatment—This consists in frequently wiping the discharges out of the canal with cotton-tipped applicators and the avoidance of irrigation, though in this method it is sometimes the practice to dip the swab in the following solution before introducing it into the ear:

R) Boric acid gr. xl	2 4
Alcohol 3j	30 0
Water to make 3ij	60.0
Label: Use in swabbing ear.		

Some men like to blow powder into the ear after the swabbing, believing that the dry powder lying against the drum attracts discharges through the

opening, boric acid is used alone or combined with 1 per cent iodine, as follows

R	Iodine (crystals)	gr	v	o	3
	Boric acid	5j		30	o
	Dissolve iodine in alcohol, make into paste with the boric acid and dry to a powder				
	Label To be used in ear as directed				

Protecting External Ear—Dermatitis may arise as a result of the irritating effects of the discharges. Washing the ear once or twice daily with normal saline (in the home, a teaspoonful of salt to the pint of water) and keeping it covered with a layer of zinc oxide ointment U.S.P. will likely prevent this.

The Sulfonamides—There can be no doubt of the great value of the drugs of this group in shortening the duration of an uncomplicated otitis media and in lessening the occurrence of complications. For example, Bowers (1940) cites 231 cases under daily observation at St. Luke's Hospital in New York, in the 113 cases in which chemotherapy was employed the average duration of the discharge was nine days, in the 118 untreated controls it was seventeen days—thus a reduction of approximately 50 per cent was accomplished. Again, in the matter of mastoidectomies 387 cases were observed, in none of which the ear condition was of more than a few days duration before admission, in 12 (5.7 per cent) of the 207 treated with chemotherapy mastoidectomy was necessary, whereas it had to be performed in 24 (11 per cent) of the 180 cases not so treated—Bowers says, therefore, that when the drug is given early, before mastoid softening occurs, the number of cases requiring operation is reduced one half. Bowers preferred sulfanilamide, which is discussed in detail regarding dosage, etc., in *Sepsis*; there is a special chapter on Sulfonamide Toxicity at the end of the book.

However, there is a small colored gentleman in the woodpile here for the employment of the new chemotherapy may yield very deceptive results. For example, a patient's discharge may cease without mastoid tenderness having ever appeared, the drug will be stopped and he will be discharged only to have him come back after some days with a high temperature and signs of serious mastoid involvement. The only remedy I have heard or seen for this state of affairs is to persist in the use of the drug for at least a week after disappearance of symptoms before signing the patient out. The other serious feature of this therapy is that under inadequate dosage the clinical picture may indicate improvement while the mastoid bone is being involved with few or no signs or symptoms to indicate it. I am sure that Bowers voices the consensus when he says that in doubtful cases it is well to stop administration of the drug for a while in order to get the true clinical picture.

Mastoiditis—When a surgical consultant concludes that the mastoid is involved he will usually have had the following points in mind as he made his examinations: (a) Tenderness over the antrum from the very beginning is not unusual but it typically stops when good drainage is established, if it continues and grows worse it means serious mastoid disease. (b) When mastoid pain begins after the ear has been discharging painlessly for two or three weeks it is indicative of acute mastoiditis, such pain appearing after the discharge has ceased has the same meaning. (c) Mastoid pain is usually

worse at night (d) A profuse discharge persisting and with pulsation is of serious moment (e) In adults with mastoid involvement there may be little tenderness

When in the surgeon's opinion operation is indicated every effort should be made to win the family's early consent because delay may endanger life, whereas with an operation performed in time the usual result of the mastoid complication is only to postpone somewhat the ultimate and complete recovery

Chronic Suppuration—These cases tax the skill and require all the experience of competent specialists and therefore the general man should not attempt to handle them at all

DENGUE

(Breakbone Fever)

Dengue is an acute infectious but not contagious disease which occurs endemically and sometimes epidemically in warm countries Boylon, of Java, first described it in 1779, and the American, Benjamin Rush, in 1780 Graham, in Beyrouth, Syria, in 1893, first suggested that it is mosquito borne and Cleland, Bradley and McDonald, working in Sydney, Australia, in 1916-19, clearly showed it to be transmitted by the yellow fever mosquito, *Aedes aegypti*, Ashburn and Craig, in 1927, proved that it is caused by a filtrable virus Some observers feel that a "reservoir" may be maintained in some of the lower animals In the Philippines, where the dengue morbidity rate is high for American troops and *Aedes albopictus* likely acts as vector, much in regard to the transmission of the disease, its incubation period, and immunity has been brought to light (see Siler, Hall and Hitchens, Holt and Kintner, Simmons, St John and Reynolds, in Bibliography) In Florida, *Aedes taeniorhynchus* is suspect upon epidemiological grounds Dengue has several times been epidemic in the southern United States, the 1922 epidemic having assumed enormous proportions, Levy says that there were 500,000 cases in Texas between June and December In the Greek epidemic of 1928, there developed 239,000 cases in Athens alone in one month The disease is usually not very difficult to diagnose for it never develops in the absence of mosquitoes (the small group of cases reported in San Francisco by Cheney [1935] is admittedly open to doubt because the vector has never been seen there) and consequently is never present after frost However, yellow fever must always be borne in mind, and some quite competent observers maintain that dengue is an abortive form of this disease, though it seems to me that the evidence is insufficient The characteristic onset is sudden, with severe headache and pain behind the eyeballs, muscle and joint ache and usually excruciating backache (all much aggravated by movement), extreme prostration, suffusion and perhaps swelling of the face, and a rapid rise of temperature and pulse rate The complications are many and diverse On the third day the temperature falls rapidly, usually accompanied by sweats, diuresis and nosebleed, and the patient feels much improved However, on

the fifth to seventh day the process recurs and there is usually a third definite attack also. During the second effervescence a rash of varied character appears on the body in most cases, Manson Bahr (1940) says it usually commences on the palms and backs of the hands and describes it as 'midway between scarlet fever and measles.' Castellani (1939) avers that in about half the cases he finds enlargement of the superficial cervical glands and sometimes also the axillary and inguinal. The second and third attacks are milder than the first, sometimes, however, the intermissions do not occur and thus the characteristic "saddle back" temperature curve is not seen. A fourth attack is extremely rare. Convalescence is often quite protracted. During the period of desquamation there is characteristically a slowing of the pulse rate and a pronounced leukopenia. Usually the individual suffers but one attack during an epidemic but this is by no means the rule. Native populations seem to have developed a high degree of immunity. In others apparently one bout of dengue confers immunity of about a year's duration.

THERAPY

Here, as in its kindred affection yellow fever, we have an endemic and epidemic mosquito borne disease which, in its characteristic symptoms and capacity for debilitating at a stroke large numbers of persons, cries aloud for specific therapy. But in vain. Indeed, because the disease itself is rarely fatal except through complications in aged and debilitated individuals and in pregnant women, evidence of serious application to a study of its symptomatic treatment is all but lacking in the literature. One reads that salicylates give great relief from pain though sometimes morphine is necessary (Le Gac and Servant [1939] say that lumbar puncture relieves the severe headache), that the bowels should be "freely opened" and 'fever treatment' applied, that the heart should be guarded against severe strain during convalescence.

All attempts at protective vaccination have so far met with failure.

DIPHTHERIA

Diphtheria is an acute infectious and contagious disease caused by *Corynebacterium diphtheriae*, which is endemic in larger centers and often becomes epidemic during the winter months. It occurs chiefly in children and is much less often food borne (milk or milk products) than is scarlet fever. The incubation period is two to five days. In the beginning of the attack the patient is but moderately indisposed, having a little soreness of the throat and slight elevation of temperature. However, the typical membrane soon begins to form in the throat and by the third or fourth day is quite thick and may cover a considerable part of the fauces. Absorption of toxins from the local lesion gives rise to profound constitutional symptoms, and there may be definite degeneration of the heart muscle, kidneys and peripheral nerves. Bronchopneumonia is a complication in nearly all the fatal cases.

Average cases, if properly treated with antitoxin, show a rapid subsidence of severe symptoms and are fully convalescent in seven to ten days. In especially virulent cases, or those not properly treated, the symptoms may gradually increase in intensity to about the sixth day, when there will be considerable obstruction to the nose and throat by the spreading membrane, a massive cervical adenitis and cellulitis, rapid and feeble pulse, and perhaps subnormal temperature. Then coma supervenes upon the profound sepsis and finally death. In that type of the disease in which the membrane first appears in the posterior part of the nasal cavity, and in the laryngeal type where the symptoms are respiratory from the beginning, the prognosis is especially poor. The chief laboratory aid to diagnosis is still the growing of the organisms in Loeffler's medium, either upon the slant overnight or upon the swab in the physician's pocket in a shorter period of time, for unfortunately the tellurite 'bedside' test has not yet proved its worth.

According to the Babylonian Talmud (352-427 A D.), the ancient Hebrews so much feared diphtheria that upon the discovery of the first case in a community the *shofar* was blown (for all other contagious diseases it was sounded only after the third case was reported). The classical description was that of Aretaeus the Cappadocian (circa 100 A D.). Aetius, in the sixth century, mentions paralysis of the palate as a sequel. A number of epidemics of the Middle Ages were described by prelates of the period, during the Renaissance and well up into the eighteenth century the Spaniards and Italians particularly concerned themselves with the description of diphtheria. I believe that the first recorded cases in America occurred in Massachusetts in 1659. To me it seems a strange thing that the diminished liability to the disease after adolescence was apparently not mentioned in the literature before the publication of Heberden's famous Commentaries in 1802. Bretonneau gave the disease its present name in 1826, but the laryngeal and pharyngeal types were not recognized as being the same malady until 1880. In 1883-84, Klebs and Loeffler identified and proved the causal relation of the organism. Von Behring developed antitoxin from the laboratory side and Roux from the practical in 1894, the former worker introduced toxin-antitoxin immunization in 1913, and Schick introduced his test in that year also. The present pandemic developed in the middle of the last century and has reached all parts of the world, though it is unquestionably very much more prevalent in colder climates especially the north temperate zone, than in the tropics. A little before the turn of the century a slight decline in incidence set in but the rate has not fallen generally and in recent years has risen in some parts of Austria, Germany, Scandinavia, Great Britain and Ireland. In these countries there has undoubtedly been an increase in the severity of the disease also, extremely malignant cases, only sporadically seen in America, occurring so frequently that before the outbreak of World War II an attempt was being made with apparent success to determine a definite correlation between the severity of the disease and the type (*gravis*, *mitis*, and *intermedius*) of infecting organism. Throughout the world as a whole mortality has considerably diminished, however, and it is but a question of time until the newer immunization methods will effect a similar reduction in the world morbidity figures. In the United States in 1939, in 88 representative cities with a total population of 38,624,731, there were only 319 deaths from diphtheria and in 52 of these cities (the largest

of which was my own city of Milwaukee, with a population of approximately 587,000) there were no deaths at all

THERAPY

Antitoxin Treatment—Before the discovery of antitoxin the mortality from diphtheria was about 45 per cent, since its use this figure has been gradually reduced, and now varies between 5 and 10 per cent. Its efficiency depends upon the administration of a sufficient dose as soon as possible to prevent the action of the toxin upon the heart and nervous system. If treated with antitoxin within the first twenty-four hours nearly every patient can be saved. Delay of two, three or four days may mean irreparable injury to vital organs by the absorbed toxin which cannot be neutralized by subsequent administration of even enormous doses of antitoxin. The data taken from her (quoted by Zingher), are well displayed in the following table (Table 2)

TABLE 2—RELATION OF MORTALITY IN DIPHTHERIA TO TIME OF ADMINISTRATION OF ANTITOXIN

Day of illness	Number of patients	Deaths	Percentage of mortality
First	329	0	1.02
Second	2269	77	3.39
Third	2407	163	6.82
Fourth	1612	176	10.91
Fifth	911	156	14.02
Sixth	416	54	12.98
Seventh	320	53	16.56
Later	327	50	15.29
Total	8591	716	8.33

The first injection should be large enough to control the disease. One large dose given early is far more efficacious than the same amount in divided doses. The usual site for subcutaneous injection is the infrascapular region; for intramuscular injection the outer aspect of the thigh about at the junction of its middle and upper thirds. Very sick patients, those who have received antitoxin only after delay, or patients in whom the disease is progressive because of an insufficient first dose should be given a large intravenous injection whenever feasible. In this way the full value of the antitoxin is obtained at once, the absorption from the subcutaneous injection is so slow that many hours must elapse before any great amount of antitoxin finds its way into the general circulation.

The following table (Table 3) gives the doses recommended by the New York City Department of Health, elsewhere in this and other countries doses twice this size are often given, but it has not been shown that the results are better than with the dosage stated in the table.

Cases of laryngeal diphtheria, moderate cases seen late at the time of the first injection, and cases of diphtheria occurring as a complication of the exanthemata should be classified and treated as 'severe' cases.

TABLE 3—AMOUNT OF ANTITOXIN REQUIRED IN THE TREATMENT OF DIPHTHERIA

	Mild cases	Moderate	Severe *	Malignant *
Infants 10 to 30 pounds in weight (under two years)	2 000 units to 3 000 units	3 000 units to 5 000 units	5 000 units to 10 000 units	7,500 units to 10 000 units
Children 30 to 90 pounds in weight (under fifteen years)	3 000 units to 4 000 units	4 000 units to 10 000 units	10 000 units to 15 000 units	10 000 units to 20 000 units
Adults 90 pounds and over in weight.	3 000 units to 5 000 units	5 000 units to 10 000 units	10 000 units to 20 000 units	20 000 units to 40 000 units

* When given intravenously one half the amount stated

In all cases a single dose of the proper amount, as indicated in the schedule, is recommended

It is recommended that the methods of administration be as follows

Mild cases subcutaneous or intramuscular

Moderate cases intramuscular or subcutaneous

Severe cases intravenous or intramuscular

Malignant cases intravenous

When the antitoxin has been administered early enough and in sufficient dose to be fully effective, a striking improvement is soon seen as manifested by a fall in temperature and a favorable change in the character of the cardiac and nervous symptoms. Within twenty-four hours of the injection of the antitoxin the membrane stops spreading, begins to soften and loosen and the swelling of the mucosa subsides. Zingher wrote: "In some cases the membrane apparently spreads and the alarmed physician is tempted to give a second dose of antitoxin. What has really happened, however, is that the area of mucous membrane which corresponds to the extending portion of false membrane has been injured by the toxin previous to the injection of the antitoxin and the appearance of the fibrinous exudate is simply the later manifestation of the damage that has already taken place."

Deleterious Effects of Antitoxin Injections—In a rather large proportion of cases an urticarial rash with a slight rise in temperature occurs from two to seven days after the injection, rarely other types of rash with more severe constitutional symptoms. Entirely distinct from these slight effects, from which recovery always ensues, are occasionally severe anaphylactic reactions. Park wrote: "A few minutes after an injection about one in every thousand persons develops a rapid and feeble pulse, nausea and a feeling of suffocation. With stimulation and, if necessary, artificial respiration, recovery soon ensues. Those who frequently suffer from attacks of asthma are liable to an attack after an antitoxin injection. There have also been recorded a few deaths. These have occurred chiefly and perhaps wholly in cases of status lymphaticus. About one death has occurred for every 70 000 persons injected and these deaths, with possibly two exceptions, have followed the first serum injection. The fear of repeating a serum injection because of having sensitized the patient is almost wholly groundless. There need be no fear in giving a

second intramuscular or subcutaneous injection to any person who has not suffered severely from the first. The only difference in the effects of the two injections will be that the serum reaction will follow almost immediately the second injection."

An intravenous injection may be followed by a chill and an accompanying rise of temperature lasting about two hours. Osgood has shown that the liability to chill is slightly greater when the antitoxin has been diluted with saline solution before injecting. If a second injection is given intravenously after a considerable lapse of time, it should be given even more slowly than the first.

Patients who have a history of asthma and are suspected of being hypersensitive to horse serum, or who have had antitoxin some time previously, should be given a preliminary intradermal test: a minute amount of the antitoxin diluted 1:10 with sterile salt solution is injected intradermally on the flexor surface of the forearm. Individuals who are unusually susceptible to horse serum will show within twenty minutes, at the site of the test, a large urticarial wheal surrounded by a distinct areola. In these cases administration should proceed as follows, the injections being made at twenty minute intervals: 0.1 cc (diluted 1:10) intradermally, 0.1 cc (diluted 1:10) subcutaneously, 0.5 cc (diluted 1:10) subcutaneously, 1 cc (diluted 1:10) subcutaneously, 0.5 cc (undiluted) intradermally, 0.5 cc (undiluted) subcutaneously, 0.5 cc (undiluted) intramuscularly, the remainder in 1 cc doses (undiluted) intramuscularly.

All of these reactions are becoming less frequent because in the refined and concentrated antitoxins now obtainable the constituents of the serum or plasma other than the antitoxin bearing globulins have been largely removed. One cc of epinephrine hydrochloride, 1:1000 solution, is useful in combating the alarming symptoms.

Dextrose in Severe Cases—In America it is exceptional for a case of diphtheria not to respond to antitoxin given early and in adequate dosage, but it is common hospital experience to encounter such failures in cases that have come under treatment too late. Abroad, as previously mentioned, cases with overwhelming toxemia from the very beginning are being seen with distressing frequency. In 1930 Schwentker and Noel confirmed the observations of others and added evidence of their own to show that profound changes in carbohydrate metabolism in the human are caused by the toxin in these severe cases, exhaustion of glycogen from the liver and specialized conducting tissue of the heart with a simultaneous rise in blood sugar, sometimes followed by a period of hypoglycemia, then a final hyperglycemia due to toxic depression of the pancreas and other sources of insulin supply. Benn, Hughes and Alstead have shown that following intravenous injection of dextrose solution in these cases the delayed return of the blood sugar curve to normal is comparable to what occurs in diabetes; they reported a series of hypertoxic cases in which the use of dextrose and insulin to supplement antitoxin resulted in a notable reduction in mortality. Begg and Harries (1935), of the same group, have confirmed the findings as to the importance of dextrose administration but are no longer convinced of the value of including the use of insulin, an important conclusion since the injection of insulin without adequate laboratory control might easily result in a hypoglycemic reaction being mistaken for a cerebral complication of the disease.

Hoyne (1936) has instituted the following routine at the Chicago Municipal Contagious and Cook County Contagious Disease Hospitals with an apparently fine effect upon the death rate

(a) *Selection of Cases*—Dextrose is given to all patients in any of the following groups (1) ill more than three days before receiving antitoxin, (2) those having the type of cervical adenitis commonly known as "bull neck," irrespective of the day in the course of the disease that antitoxin was administered, (3) those with marked albuminuria, (4) all postnasal and all other malignant types of any character

(b) *Dosage*—Five hundred to 1000 cc of 10 per cent solution by the gravity method

(c) *Repetition*—Once daily for at least eight days

The Sulfonamides—Fisher (1940) reports the successful treatment of a small series of cases with sulfanilamide, but with such a doughty and venerable specific as antitoxin available it would certainly seem to me unwise to undertake a shift to chemotherapy save perhaps in markedly serum sensitive individuals

Cevitamic Acid—Since cevitamic acid (vitamin C) may be isolated from the adrenal glands and these glands have long been known to suffer in diphtheria, it has been thought that possibly the administration of large amounts of this vitamin might be worthwhile in severe cases, but Dieckhoff and Schuler (1938), did not find it so from the standpoint of either complications or mortality Pakter and Schick (1938) also found that cevitamic acid was unable to alter positive Schick tests

Cardiac Complications—It is doubtless true that heart failure is today the most common cause of death in diphtheria *practically all these deaths occur in cases in which antitoxin has been withheld too long or given in too feeble dose* The usual circulatory stimulants are of little avail here, and because of the degenerative changes in the heart muscle digitalis is looked upon as contraindicated Hoyne believes that the dextrose treatment (see above) has been effective in preventing myocarditis in many instances Of course the patient must be kept without pillows fed through a glass tube and not allowed to rise even partially from the prone position for any purpose whatsoever Pointing out that restlessness is the most important and constant warning sign of increasing obstruction and anoxemia, Neffson and Wishik (1934) counsel against the use of strong sedative drugs, for sedation they give whiskey, 1 drachm (4 cc.) per year up to ½ ounce (15 cc.), diluted with water, sweetened with sugar and given every three hours

It is the part of wisdom to continue heart vigilance for several weeks following diphtheria and even though the patient has to all appearances grown strong to insist that he return gradually to full physical activity. Burkhardt, Eggleston and Smith (1938) feel that where possible electrocardiographic studies should be made and complete inactivity be enforced until the electrocardiogram has returned to normal. Wesselhoeft (1941) also advocates an increased routine employment of the electrocardiograph in diphtheria wards

Local Treatment—The nose and throat are nowadays left very much alone, though a gargle or spray of saline or Dobell's solution is sometimes employed Wesselhoeft says that hot glucose irrigation of the throat every three hours greatly reduces the foul odor in a diphtheria ward, if done very

gently it is apparently very soothing. Many men like to use a steamy inhalant (see Common Cold) for its soothing effect on the mucosa; perhaps it is best here to omit drugs and use just the steam alone. Neffsoo and Wishik believe the expectorant action of syrup of *Lipicac* may aid in loosening the membrane in severe cases. 10 minims to 1 drachm (0.6-4 cc), depending upon age, every three hours.

Diet—If vomiting has supervened all mouth feeding must cease and sole reliance be placed upon the intravenous administration of dextrose if much fluid is being lost; dissolve the dextrose in Locke's solution instead of water to make up the loss in salts. Many young children refuse all food in the severe cases even if not vomiting; if possible they should be got to take some milk which may be fortified with cream or it may be offered in the form of *egg-nog* which is very nourishing. The following *egg-nog* contains no mixture of liquors and only one fourth as much alcohol as the familiar beverage: to the well beaten yolk of an egg add the following with stirring— $\frac{1}{2}$ pint milk, 6 teaspoonfuls brandy and a level teaspoonful of sugar. This should be offered for a few sips at frequent intervals during several hours. The addition of a small amount of nutmeg is pleasing to adults but not always to children; the white of the egg beaten with a little sugar and placed on top makes the whole more appealing especially if dusted with nutmeg.

As soon as possible the patient should be placed upon such a diet as that described in Common Cold.

The Period of Quarantine—The patient should be kept isolated until two successive nose and throat cultures prove negative. Attempts to lessen the length of this period are usually made by the employment of Dobell's solution and other mild antiseptics. If the cultures continue positive for several weeks guinea pig inoculations should be made to determine the virulence of the organisms. I believe it is now conceded that the use of lactic acid organisms in the spray or naturally soured milk as a gargle only hasten the disappearance of the diphtheritic membrane but do not produce cultures negative to *Bacillus diphtheriae*.

Paralysis—In general the various types of paralysis so commonly associated with diphtheria are estimated to occur in from 10 to 20 per cent of all the cases. That of the swallowing muscles which sometimes occurs at the height of a severe case requires nasal or parenteral feeding. Diaphragmatic paralysis is rare and nearly always fatal. The more usual type of postdiphtheritic paralysis that of the arms or legs comes on in from one to six or seven weeks and is usually transient. Recovery may be hastened by massage and the use of strychnine sulfate in tonic doses. As this condition sometimes precedes late cardiac failure the patients should be kept perfectly quiet. Of course antitoxin big and early will prevent these paralyzes in those appearing after convalescence is established it is not indicated.

Emergency Relief in Laryngeal Cases—The dyspnea is caused by one or more of the following: a partially detached membrane which has been drawn down into the lumen of the glottis; obstruction by tenacious mucopurulent secretion; edema of the inflamed subglottic tissues; spasm of the glottis. The measures available for the relief of this very serious condition—removal of membrane with forceps or with an applicator introduced through the laryngoscope; intubation; tracheotomy; aspiration—will not be described here as

they are all highly specialized procedures which can only be learned upon the cadaver and in the ward and not from the pages of a book.

The Carrier.—The gamut of antiseptic sprays, gargles, swabs, and snuffing powders (including the sulfonamides) has been run and it is now the consensus that simple local cleanliness, best promoted by spraying and gargling with normal saline solution, will accomplish whatever is to be hoped for (which is practically nothing!) from local treatment. Tonsillectomy is said to be often helpful.

PROPHYLAXIS

Who Should Be Immunized and When—Before the age of six months many babies are protected against diphtheria if their mothers are immune, but fully 95 per cent of children are susceptible when they reach the age of one year, as indicated by the Schick test (It might be noted in passing that Grozin [1939] is urging the greater simplicity and sensitiveness of the Reh scratch test.) From that time on susceptibility slowly declines, as "natural" immunity is slowly acquired until at the age of seventeen only about 18 per cent are susceptible. Beyond this age susceptibility does not seem to decrease for from 10 to 20 per cent of adults show a positive Schick reaction (10 per cent in Pygott's [1938] series of recovered individuals showed a positive reaction after six or more weeks). These figures are true only for individuals living in the more crowded cities, in rural sections the percentage of susceptibility is much higher for both children and adults. Zingher stated some years ago that among nurses coming into training schools from small towns and rural sections, the Schick test was positive in 40 to 80 per cent. Now, since over 80 per cent of all cases of diphtheria occur in children under the age of ten, and over 64 per cent of all cases and 80 per cent of all deaths occur in children under the age of five and since almost 100 per cent of children receiving proper prophylactic treatment become immune, the very clear professional duty is to immunize all children as young as possible. In most cities nowadays the public health authorities are assiduously immunizing school children but responsibility for immunizing the even more susceptible group from six months to six years still rests with the general practitioner. The task is somewhat simplified by the fact that the Schick test may be omitted for the reason that these youngsters are practically all susceptible, but the point of just when best to set about the immunization has been a rather delicate one except that there is general agreement that it should take place somewhere between the ages of six months and one year.

Blum has shown that a variable proportion of infants retain the passive immunity inherited from their mothers as long as nine months, therefore in a group injected before this time some individuals will not be protected because of the inability to graft an active immunity upon a preexisting passive one. From their studies, Greengard and Bernstein (1935) concluded that if immunization is to be carried out at six months preliminary Schick tests should be done and only the positive reactors inoculated, the negatives being retested and the new positives injected when they appear. Otherwise, routine immunization should be withheld until between nine and twelve months, when practically all babies will have lost their passive immunity. These findings accord with the belief of most pediatricians that the best time to inoculate is toward the close of the first year. (For a comprehensive immunization schedule see Smallpox.)

Just before the outbreak of World War II, France became the first major nation to make diphtheria immunization compulsory.

Preparations Available—The first standardized preparation used was the toxin antitoxin of von Behring—a diphtheria toxin neutralized by antitoxin so that the toxic properties were lost but the antigenic properties remained. It was highly effective but had to be given three times at intervals of a week and there was always some slight danger of serum sensitization with it because of the small amount of horse serum it contained. Severe local and general reactions were fairly frequent in older children and adults and the product was relatively unstable and therefore always had to be used as fresh as possible. This preparation was almost entirely replaced throughout the world by the toxoid developed by Ramon, a diphtheria toxin modified by the addition of 3 to 4 per cent of commercial solution of formaldehyde and incubated at from 38° to 40° C for four to six weeks. Like toxin antitoxin it has lost its toxicity but retained its antigenic properties. Some local and general reactions to this toxoid occur (see below), but it contains no horse or other serum and therefore cannot cause serum sensitization and its effectiveness is considered to be much higher than that of toxin antitoxin. The next product to be given extensive practical trial was alum precipitated toxoid which resulted from the work of Glenny and Havens and their associates and was developed clinically principally by Graham, Murphree and Gill, Baker and Gill, Saunders, McGinnes, Stebbins and Hart, and Keller and Leathers. It is a toxoid whose rate of absorption has been slowed by precipitation with alum, the advantage of this lying in the fact that less antigen is lost by excretion and therefore complete immunization might theoretically be accomplished with one injection. The incidence of local and general reactions (see below) is less than with toxoid and serum sensitization is no more to be feared with it than with toxoid.

During the years in which this immunization work has been developing trials have been made of mixtures made with goat and sheep serum but these preparations have been outmoded by the newer ones. The toxin sodium ricinoleate method of Larsen and the percutaneous method of Lowenstein have not won places for themselves. The method of Jensen (1937), in which a single injection of toxoid is followed by nasal instillations of the same agent, has not yet had extensive trial.

Alum precipitated Toxoid—This preparation is injected subcutaneously at the deltoid insertion in a dose of 0.5 or 1 cc., depending upon which manufacturer's product is being used, usually in the past only one injection has been given, but Hoyne (1939), with a large contagious disease experience in Chicago, advocates a second injection of the same size three or four weeks after the first, and I find that many men are routinely giving this second injection nowadays. Being an insoluble substance it raises a firm nodule at the site of injection and around it there appears and persists for a few days a trifling inflammatory reaction, the nodule becoming smaller as the material is absorbed and disappearing completely in six weeks. Very rarely—practically never in children under two years of age—there may be more marked local redness and swelling and discomfort and sometimes malaise, anorexia, aching and a slight fever. But these reactions occur so seldom up to six or eight years of age that the possibility is usually disregarded as being of no moment except in individuals known to be definitely allergic. Kern, Crump

and Cope (1935) have shown that these latter are distinctly less likely to have unfavorable reactions if the inoculation is made intracutaneously instead of subcutaneously. Using 0.05 cc. of a preparation whose subcutaneous dose was 0.5 cc. or 0.1 cc. of a 1 cc. preparation, they were apparently able (the series was small) to accomplish as good immunization by the intracutaneous as by the subcutaneous route.

The chief objectionable feature of the alum precipitated toxoid method of immunization consists in the rather frequent occurrence of sterile abscesses at the site of injection doubtless a tissue reaction to the sterile insoluble foreign body. But this is very rare indeed in young children. In Kositz's (1935) series of 2013 immunizations no abscesses occurred in children under five years of age. In Shafston's (1936) smaller series none under the age of eight.

Toxoid (Inatoxin).—This preparation is injected subcutaneously two or three times in doses of 1 cc. each with intervals of three or four weeks between. General reactions are rare in children under eight years of age and in this group local reactions of any moment occur very infrequently, but in older children and adults the incidence of both types considerably increases. An intracutaneous test dose of 0.1 cc. of toxoid diluted with salt solution (1 in 20) is sometimes given and the toxoid then withheld from those who show a positive skin reaction (a flush of 10 mm. or more in diameter, with perhaps some slight swelling after forty-eight hours—Moloney test). Such skin test solutions are distributed with some of the commercial preparations. Experience has shown that unduly severe reactions in adults may be avoided if the regular doses are preceded by two preliminary doses of 0.1 and 0.25 cc. of the undiluted toxoid at an interval of one week.

Choice of Preparations.—A few years ago alum precipitated toxoid seemed to be preferred by most workers in the United States and England, but in Canada the use of toxoid was always persisted in and there was insistence on the full course of three injections (Fitzgerald *et al.* 1928 Benjamin *et al.* 1938). Recently in the United States Bundesen (1939) and his associates of the Chicago Board of Health have also pronounced in favor of a return to the three doses of toxoid at intervals of a month. Their comparative studies employed large numbers of children and extended over several years. In a more limited study in New Haven Hillman and Linde (1939) likewise found three-dose toxoid the most effective method. It is my impression that for diphtheria immunization alone a swing back to toxoid has set in rather generally throughout the United States but that most pediatricians nowadays are preferring the two-dose combined alum precipitated diphtheria and tetanus toxoids (see article on Tetanus and the comprehensive immunization schedule in Smallpox).

Rapidity of Immunization.—It is now considered that with either the toxoid or alum precipitated toxoid methods antitoxin begins to appear in the blood in a few days and full immunity is reached in 95 per cent or more children in four to six weeks.

Reimmunization.—Ideally all individuals should be Schick tested three to six months after immunization. The positives can then be reimmunized with reasonable assurance of success by either method. Preliminary desensitization had perhaps best precede the second trial. Fischer *et al.* (1940) point out that children tested during the febrile period of an acute infectious

disease in whom bullous Schick reactions develop should be retested some time after recovery before being considered susceptible to diphtheria

Duration of Immunity—A number of men are now urging that upon entrance into school the child be given another injection since Schick negativity several years after the original immunization does not always mean complete protection the antitoxin content per cc of blood (1/25 unit) now held necessary for such protection being much more than the minimum content (1/250) to insure Schick negativity in most instances And even Schick negativity is not retained by all children to school age, Schwartz and Janney (1938), retesting 145 children six or seven years after immunizing them with 3 doses of toxoid, found that 92 per cent had reverted to a Schick positive test Benjamin *et al* (1940) found 14.9 per cent of their larger series positive after five to eleven years which was twice the proportion positive after four to five years Reimmunization with one injection upon reaching the school age of five or six years seems a decidedly sound procedure

Tonsillectomy and Immunity—Buice's (1934) study I think convincingly indicates that tonsillectomy neither decreases the incidence of diphtheria nor increases Schick negative immunity

Prophylaxis with Antitoxin in Nonimmune Exposed Cases—I formerly it was the routine practice to give an immunizing dose of antitoxin to children who had been exposed to diphtheria and who had not been immunized Nowadays it is more customary to wait a while watching the child carefully for the early signs of the disease and then giving a suitable therapeutic dose of antitoxin should they appear This change of policy has followed the repeated observation that even a small dose of the serum may cause an alarming reaction or render the patient sensitive to a therapeutic dose subsequently administered Of course if the child cannot be watched it should be given 1000 units of ordinary treatment antitoxin as soon as possible this establishes an immediate passive immunity which lasts for about three weeks

Combined Diphtheria and Tetanus Toxoids—See article on Tetanus

Order of Immunization Against Diphtheria and Other Acute Infectious Diseases—See article on Smallpox

DYSENTERY

Nearly all the notable writers since that able Byzantine compiler, Alexander of Tralles (525-605 A.D.) have left accounts of dysentery During the Thirty Years War in the seventeenth century it ravaged the Continent and England where the great Sydenham among others described it The disease continued widely prevalent throughout the eighteenth century in Europe and following Clive's victorious campaigns the varieties encountered by British medical officers in India began to be described The etiologic agents of bacillary dysentery were discovered by the following workers Shiga in Japan (1898), Kruse in Germany (1900) Flexner in America (1900) Strong and Musgrave in the Philippines (1900) and the *Y bacillus* of Hiss and Russell in America (1903) Lambi probably saw the causative ameba of the protozoan

TABLE 4—SEVERAL ALTERNATIVE PLANS FOR THE TREATMENT OF AMEBIASIS WITH SPECIFIC DRUGS (THE DOSES ARE FOR ADULTS)

First course of treatment	Second course (To begin after ten days' rest)	Third course (After ten days' rest.)
Emetine hydrochloride (subcutaneously or intramuscularly). A total dose not to exceed 1 grain per 2 lbs body weight (10 mg per Kg). Give two thirds of the total amount in first six days, remaining one third in second six days (if not a case of moderate or considerable severity, the emetine may be omitted)	Bismuth subcarbonate (or subnitrate), three drachms (12.0 Gm) in milk or water three to five times daily	Bismuth salt may be continued as long as patient can take it
At the same time give either one of the following	At the same time either of the following depending upon which plan is being pursued.	
Plan A Carbarsone, 4 grains (0.25 Gm) twice daily by mouth for ten days	Vioform, 8 grains (0.5 Gm) twice daily by mouth for ten days (Or chiniofon, 10 grains [1 Gm] three times daily by mouth for eight days or try the chiniofon enemas see Plan D, 1st course)	Repeat the carbarsone course by mouth or try the carbarsone enemas
Plan B Vioform, 8 grains (0.5 Gm) twice daily by mouth for ten days (Or chiniofon, 10 grains [1 Gm] three times daily for eight days)	Carbarsone, 4 grains (0.25 Gm) twice daily by mouth for ten days (Or carbarsone enemas see Plan C, 1st course)	Repeat either the vioform or chiniofon course by mouth or try the chiniofon enemas.
Plan C Carbarsone, 200 cc of 1 per cent in 2 per cent sodium bicarbonate solution by rectum, repeating on alternate evenings until at least five enemas have been retained over night	Vioform, 8 grains (0.5 Gm) twice daily by mouth for ten days (Or chiniofon, 10 grains [1 Gm] three times daily by mouth for eight days, or try the chiniofon enemas, see Plan D, 1st course)	Repeat carbarsone enemas or try carbarsone by mouth
Plan D Chiniofon, 300 cc of 2.5 per cent by rectum, to be retained as long as possible, repeated daily for ten days	Carbarsone, 4 grains (0.25 Gm) twice daily by mouth for ten days (Or carbarsone enemas see Plan C, 1st course)	Repeat chiniofon enemas or try chiniofon or vioform by mouth

It is unlikely that the courses will have been pursued with only ten-day intervals, but even if they have, then ten days after completion of the third course if will be safe to repeat the emetine provided the patient experienced no reactions during the first course with this drug, thereafter the courses may be given all over again or merely continued without the second trial of emetine. Or it may be advisable at this time to try one of the other drugs or special methods of administration described in the body of the text, such as substituting duodoquin for either vioform or chiniofon or giving chiniofon enemas simultaneously with the oral administration of carbarsone, or using specac enemas or transduodenal lavages with specac or even drastic dosing with specac pills still advocated by Simon, or the De Kivas hot copper sulfate irrigations or the intestinal oxygenation method of Felsen. Of course the arsenicals and oxyquinolines do not have to be alternated in the above definite fashion, for either of them may be given safely in several consecutive courses provided there are intervals of at least ten days between and the physician is ever watchful for evidences of toxic action.

Study the details regarding all of the drugs on the following pages

affected Craig's "very conservative" estimate is that between 5 and 10 per cent of the people in the United States are infected with *Endamoeba histolytica* (Faust, 1942, feels that possibly 20 per cent is a more nearly accurate figure), since only a very small proportion of these persons are actively ill this means that the number of carriers capable of propagating amebiasis is prodigious Faust (1941) recovered the organism from the bowel in 64 per cent of 202 autopsies performed within four hours after accidental death in New Orleans

THERAPY

In what follows, the "specific" drugs are individually considered and then there is presented a chart (Table 4) offering several alternative plans for their use. The reader will please understand that this chart does not represent the practice of any single eminent individual or clinical group but has merely been put together by me in the belief that some attempt at standardization is required if the man treating an occasional case of amebiasis is to make the best use of the considerable amount of information now available. The essence of that information is that for success the organisms must be vigorously assailed by several agents and that it has to be done very carefully and cautiously—it is this which I have sought to get into the chart. Then there are discussions of diet, general and nursing care, the complications and the carrier.

IPECACUANHA AND DERIVATIVES

Emetine—There are few diseases which respond so quickly to any therapy as does amebiasis to emetine, which was introduced by Rogers in India in 1912, but it is now the consensus that it should be used only to accomplish rapid subsidence of symptoms in moderate to severe cases. The drug's limitations are that it is acutely poisonous if given in fully "effective" doses and that even in much reduced dosage cumulative poisoning may occur if short courses of its use are not separated by periods of six to eight weeks in which the drug is not given, furthermore, the ameba very likely becomes emetine fast just as the spirochete becomes arsenic fast. The dictum has been pronounced (Anderson and Leake, 1930) that dosage should be based on weight and should not exceed 1 mg ($1/60$ grain) per kilogram (2.2 pounds) for a single dose or a total dosage of 10 mg per kilogram ($\frac{1}{3}$ grain per 2.2 pounds). The practical administration would work out as follows, using emetine hydrochloride

60 Kg (132 pounds) at 10 mg per Kg = 0.6 Gm (10 grains) total dose

Give two thirds of this total amount in the first six days and the remainder in the succeeding six days

1 injection of 1 gram (0.06 Gm) daily for six days = 6 grains (0.36 Gm)

1 injection of $\frac{1}{2}$ grain (0.03 Gm) daily for six days = 3 grains (0.18 Gm)

The patient has then received 0 grains (0.54 Gm), which is sufficiently close to the theoretical limit for his size. He is not to receive emetine again, if

at all under six or preferably eight weeks, but during this period other drugs may be given.

Subcutaneous injection is not infrequently followed by pain and discoloration of the skin and very rarely even by slough, but it continues to be almost the routine method. Manson Bahr, 1940, says that fewer sequelae occur if the skin is pinched up and the drug injected *deeply* subcutaneously. Intramuscular injection deep into the gluteal region causes no discoloration, is no more painful and if retraction of the plunger has failed to draw blood up into the syringe one can be sure of not being in a vein, even so, absorption is undoubtedly faster by this route which probably causes many men to hesitate to employ it. Recently an officer in the U S Navy has reported (J A M A, 116, 9230 1941) that he is rendering his intramuscular injections painless by using a 1 to 2 per cent procaine hydrochloride solution as solvent for the drug. It would seem that toxic effects need not be feared from such a practice except in individuals hypersensitive to procaine. Emetine is said to cause very great pain when introduced in enema form, intravenous administration is regarded almost universally as unnecessarily dangerous.

Auremetine has not made a place for itself. Emetine bismuth iodide (containing 20 per cent of emetine), which may be given by mouth is sometimes substituted for emetine hydrochloride, for the adult, 1 capsule of 1 grain (0.06 Gm) three times daily for four to ten days is about as much as will be tolerated and even this dosage is usually followed by so much nausea and vomiting as to cause its early abandonment—nevertheless, Manson Bahr (1940) still prefers this drug and is dissatisfied unless there is nausea and vomiting to indicate that it is being absorbed.

Before emetine dosage was placed on a scientific basis we knew that it frequently caused an increase in diarrhea many times accompanied by nausea also there were sometimes caused rapidly, irregularly and weakness of the heart beat, asthenia, neuritis (*myositis*) and palsy, some deaths, apparently in particular fibrillation primarily induced by the drug have been reported. Some of these cases were undoubtedly instances of idiosyncrasy to the drug and many others were due to the use of greatly excessive dosage. Brown (1935), reviewing the 554 cases of the Mayo Clinic in which emetine had been used within the limits of our present dosage scheme found only three reactions in the series. Considering the high usefulness of the drug it would seem that its employment is not unduly dangerous if one is watchful and follows carefully the principles discussed above. Pregnancy, as well as cardiovascular disease is considered to contraindicate it. The chances of myocardial injury probably increase above the age of sixty, in infants emetine is not usually used.

Ipecac—The use of sufficient powdered ipecac by mouth for effective antiepileptic action is precluded because of the violent vomiting which is caused. Salol-coated pills have not been uniformly satisfactory, still as recently as 1934, Simon has stated that he resorts to these pills in patients who have resisted the other drugs—50 to 100 grains (3-6 Gm) at 9:30 P.M. This drastic treatment he feels is often completely effective.

A retention enema of ipecac is sometimes resorted to. Lawson's method is to place 60 to 120 grains (4-8 Gm) of powdered ipecac in 1½ pints (750 cc) of water which is kept hot (but not boiling) for an hour. Then when it has cooled to body temperature the whole preparation, without filtering

is introduced slowly into the rectum (previously washed out with warm water) to be retained as long as possible. Pain and tenesmus cause reduction in the volume of the enema.

Andresen has employed a transduodenal method of introducing the ipecac. Passing the Jutte tube well down into the duodenum in the morning after a twelve hour fast, or the night before where there is much pyloric spasm, the pylorus is encouraged to close by causing the patient to drink 4 or 5 ounces (120 or 150 cc) of cold milk alongside the tube. Then a pint (500 cc) of 10 per cent aqueous solution of sodium and magnesium sulfate is allowed to run slowly into the tube at 105° F (41° C), usually producing a copious watery evacuation in twenty to thirty minutes and, it is believed, cleaning out the ulcer bases. Twenty minutes after giving the salt solution, 1 drachm (4 Gm) of powdered ipecac in warm water is introduced and the tube washed with another 50 cc of water, waiting thereafter an hour before removing the tube to prevent ipecac entering the stomach and causing vomiting. One and one half to two hours after giving the ipecac frequent feedings are resumed. Seven daily treatments are given, then a week's rest and then another week of treatment. During the second week, when no treatment is being given, the patient is usually constipated and is felt to require soothing laxatives.

ORGANIC ARSENICALS

At the present time these drugs seem to stand as follows in order of decreasing usefulness: carbarsone, treparsol, and acetarsone (stovarsol). Some men of experience treat amebiasis solely with these arsenicals in courses with rest periods between, or in alternating courses with oxyquinoline derivatives or even together with one of the oxyquinolines, others precede or accompany their use by a course of emetine, especially in severe cases.

Carbarsone—A total dosage of 75 mg (1½ grains) per kilogram (2½ pounds) body weight is advised by Reed (1934), one of the chief advocates of this drug to be spread over ten days with two or three doses daily. The top dose for an adult, if we use 60 Kg (132 pounds) as the upper limit of weight to be used in calculating (as with emetine), would accordingly be 4 grains (0.25 Gm) twice daily for ten days. Given in capsules after eating this dose has been used in a great many individuals with perhaps better success than attends the use of any other drug save emetine, but considering that carbarsone can be used in two or three or even more successive courses with rest periods of only two days between—a thing wholly impossible with emetine in the light of newer knowledge—it has seriously challenged the eminent position of the classical drug. Some men are cautiously using larger dosage than the above—for example, Hakansson (1939) who has in some instances about trebled Reed's dosage—but there is general recognition that this is probably justified only in recalcitrant cases. Mateer *et al* (1940) say that in their experience at the Mayo Clinic cure is obtained in all but 10 per cent of cases with the smaller dosage but that they can reduce the number of failures to 3 per cent by giving in addition a chiniofon retention enema (see method under Chiniofon) every other morning during the ten day period.

Anderson and Reed (1934) have also made satisfactory rectal use of carbarsone. A cleansing soda enema is followed in one hour by instillation

into the rectum of 200 cc of warm 2 per cent sodium bicarbonate solution containing 1 per cent carbarsone, 3 grains (0.2 Gm) of sodium amytal having been previously given by mouth to insure sleep and facilitate retention of the enema. If the enema is expelled before morning the treatment is repeated on alternate evenings until at least five enemas have been retained over night. Such a course may replace, but should not be given at the same time as a course of the drug by mouth.

Upon the whole this drug seems to be relatively nontoxic, as indeed one would think it should be for the reason that it was not introduced into practical therapeutics until its safe dosage range had been worked out in animals (an advantage only recently enjoyed by emetine). Leake has pointed out that the similarity of its chemical arrangement to that of trypanamide might lead us to expect some injuries to the optic tract as the drug comes into more extensive use, but so far the only report has been of a moderate papillitis and retinal edema in a case of Smithies (1934). Reed has seen no such injuries in his 400 cases. Smithies' patient also had puffiness of the eyelids and face and albuminuria with granular casts; another patient had laryngeal and pulmonary edema, sore throat, sneezing and lacrimation, and another developed exfoliative dermatitis limited to the hands and arms. Epstein (1936) reported the case of a patient who died from arsenical exfoliative dermatitis apparently induced by doses of the drug within the therapeutic range; autopsy revealed acute fatty degeneration of the liver, which gives point to Reed's (1934) recommendation of the use of liver function tests before prescribing carbarsone. The drug should be withdrawn in patients who experience gastrointestinal irritation, congestion of the respiratory tract, visual disturbances, jaundice, neuritis, pruritus or skin eruptions; frequent examinations should be made to detect enlargement of the liver or spleen or evidences of renal damage.

Treparsol.—The adult dose of this drug is 4 grains (0.25 Gm) in capsules three times daily after meals for four days; two or more such courses may be given with rest periods of ten days between. The signs of intolerance would be the same as those noted for carbarsone (above) except that optic tract damage is not to be expected. Brown (1935) used treparsol satisfactorily in 301 cases with no deaths attributable to the drug but such have been recorded elsewhere; erythema occurred in 2.6 per cent of his cases and 1 patient had nausea and vomiting, the symptoms in all instances subsiding in three to five days after the withdrawal of the drug. Carbarsone has almost completely replaced this drug.

Acetarsone (Stovarsol, Spirincide).—The adult dose of this drug is 4 grains (0.25 Gm) three times daily after meals for seven days with seven day intervals between courses. Following the original publication of Marchoux a considerable literature testified to the effectiveness of acetarsone as an amebicide, but unfortunately the incidence of toxic arsenical reactions (see Carbarsone, above) was found to be high (Bender, 1927; Anderson and Leake, 1930). Brown (1934) gave the drug a fair chance before giving it up; in his 232 cases there were no deaths but toxic erythema, sometimes true exfoliative dermatitis, occurred in 5.6 per cent of the cases; there were also 2 instances of severe neuritis, one lasting almost a year. Segal (1940) has reported a case of hemorrhagic encephalopathy following the use of acetarsone.

OXYQUINOLINE DERIVATIVES

Chiniofon (Yatren, Anayodin) —This, the older of the three drugs of the group, has been employed quite extensively in the tropics. In the continental United States, O Connor and Hulse (1935) have perhaps had the largest experience with it, their series comprises 152 cases and upon the whole the results have been very satisfactory. To adults they give 4 pills of 4 grains (0.25 Gm) each three times daily with meals for eight days, in some instances the diarrhea is increased and there is a scalding sensation during defecation, necessitating reduction to 3 or 2 pills per dose, but treatment is always continued until the full course of 96 pills has been given. During or following such treatment these observers have encountered no toxic symptoms nor do they know of any in the experience of their colleagues who use the drug. Fatalities have been reported following the intravenous administration of chiniofon, but they are of no significance in the present connection.

Chiniofon may also be given by rectum. Willoughby and Aslett (1931) report the very successful treatment of 150 cases, giving 10 ounces (300 cc) of 2.5 per cent solution of the drug preceded by one hour by a 1 pint (500 cc) enema of 2 per cent sodium bicarbonate solution, the chiniofon enema is retained as long as possible the procedure being repeated daily for ten days. It is best not to give the drug by rectum and by mouth at the same time. Mateer *et al* (1940) give a cleansing saline enema and then introduce the chiniofon solution with the patient in the knee-chest position, after five minutes the following positions are taken in succession, each being held for thirty minutes: right side, back, left side, back. At the outset of the treatment, paregoric is given at frequent intervals if necessary to ensure retention of the enema.

Manson-Bahr's (1940) preferred treatment is the simultaneous administration of chiniofon by rectum and emetine bismuth iodide by mouth.

Vioform —David *et al* (1933) have studied this drug which differs from chiniofon in containing chlorine and considerably more iodine. Most of their adult patients received a 4 grain (0.25 Gm) capsule three times daily with meals for ten days. After a ten-day rest the course was repeated. Results were satisfactory. Anderson and Reed (1934), of the same group of investigators, reported that of the 60 patients treated, 1 experienced palpitation, dyspnea, a sense of fullness in the head and headache and 2 others had gastrointestinal upsets, one very severe. Reed (1934) later stated that the gastrointestinal symptoms are largely avoided by using the enteric-coated capsules now available, at that time he advised giving 8 grains (0.5 Gm) twice daily for ten days and repeating the course as often as needed with ten-day intervals.

Vioform is not used rectally.

Diodoquin —There have been a few reports of the use of this drug. Hummel (1939) has given three tablets of $3\frac{1}{2}$ grains (0.21 Gm) three times daily for twenty days to a small group of patients with very good results and no toxic reactions. Diodoquin is said to contain considerably more iodine than either chiniofon or vioform and would seem to deserve more extensive clinical trial since it has been shown to be very effective in experimental animals.

MISCELLANEOUS DRUGS

Bismuth Subnitrate (or Subcarbonate?).—James and the late Dr. Deeks, of the United Fruit Company Medical Service, have long advocated large

doses of bismuth subnitrate in conjunction with other therapy—a heaping teaspoonful well mixed with milk or water three to five times daily. Or some such preparation as that in the prescription below might be used. Others have also found this a very satisfactory adjuvant medication (Shattuck, 1939, thinks that a preliminary purge with castor oil, bed rest, and a generous but strict milk diet are important adjuncts of this treatment) but the recent tendency has been to substitute the subcarbonate salt because of the frequent secondary bacterial colitis thought to make conditions ideal for the occurrence of nitrite poisoning, however, James (1934) deprecates this since he early found the subcarbonate not to be so effective as the subnitrate.

R	Bismuth subcarbonate	℥vj	180 0
	Sodium bicarbonate	℥j	30 0
	Mix and divide into 30 powder papers (blue)		
	Tartaric acid	℥j	30 0
	Divide into 30 powder papers (white)		
	Label: Stir contents of 2 blue papers in half glass of water, dissolve con- tents of 2 white papers in separate half glass of water, mix the two and drink while effervescing		

Soper (1934) has found that when secondary ulcers develop just above the internal sphincter, as in most of the "carriers" of his experience, the powder insufflation method (using equal parts of bismuth subcarbonate and calomel through a powder blower) is of great value.

Chaparro Amargoso (and Castamargina).—The merits of chaparro as an amebicide were well established by Nixon many years ago. The whole plant is boiled in water for thirty to sixty minutes and 6 to 8 ounces (180–240 cc) of the infusion, which should have the color of weak tea, are given by mouth before meals and on retiring, it may also be introduced once or twice daily as a retention enema. While in Mexico City in 1934 I found that a solution of castamargina, the active glucosidal principle which has been isolated there, was being employed as an interval drug between courses of more drastic therapy. It seems to me unlikely that this drug will compete successfully with the previously described agents, I am unaware of any thorough modern study of it.

Kosam.—This seed, which is an old oriental remedy for diarrhea, was reintroduced by Liu a few years ago. However, Kuzett *et al* (1941) found it a gastric irritant and the symptomatic benefits it conferred in cases resistant to other amebicides were only fleeting or temporary.

Oil of *Chenopodium*.—Two cc of this drug are given together with 1½ ounces of castor oil at a single dose. Or the oil may be emulsified with acacia and administered by rectum, the anal mucosa being protected with petrolatum and terminating the injection with 2 ounces of inert oil. The buttocks should be elevated, the enema given slowly and with great care, the first dose not exceeding 8 ounces in the adult, it is to be retained for an hour if possible.

Barnes and Cort reported a series of cases from Siam in which the results were as good as those obtained by the use of emetine. In working among native populations, the two oils already combined can be sent to distant patients who could not otherwise be reached by treatment. A point to be remembered is that oil of *chenopodium* should not be repeated in full dose in less than two or three weeks because of the possibility of renal irritation.

Quinine—Quinine has been used for a long time for rectal irrigations with more or less success. One or 2 liters of 1 : 2500 to 1 : 1000 aqueous solution of the sulfate are employed. Quite severe cinchonism not infrequently follows its use by this route. Brooke has employed quinine sulfate satisfactorily by mouth, giving 20 to 30 grains daily for six days and repeating after an interval of a week.

Salicylic Acid—This drug is used in the form of a 2 per cent solution of sodium salicylate by rectal enema. Lutsch, in Africa, extols the method for the prompt relief of pain and tenesmus. He gives 5 grains (0.3 Gm.) of ealomel and allows nothing but barley water the first day and later a little boiled milk. Six hours afterward he gives the enema and repeats it the second and fourth or third and fifth days. It should be retained for half an hour. For a child a year old he uses only 90 cc. of the solution, for the adult about 650 cc.

Copper Sulfate—The De Rivas treatment in use in several tropical countries (Hemenway 1934, Beregoff 1935, De Rivas 1938) consists in the use of hot rectal irrigations of copper sulfate solution given through a stomach tube inserted into the rectum and connected by a glass Y tube to the enema vessel and a waste pail. As the tube is slowly inserted sufficient fluid is admitted to balloon out the intestine so that the tube may be pushed up into the ascending and transverse colon, then a rectal thermometer is inserted. From 1 to 2 liters of a 1 : 5000 copper sulfate solution at 52° to 55° C (125° to 131° F), with 1 ounce (30 cc.) of glycerin per liter, are allowed to flow into the colon at 150 cc. a minute. When there is pain the enema tube is clamped off, that to the pail opened and some of the solution allowed to flow out. After this treatment is continued and at the close the patient holds the fluid as long as possible. The treatments are given three times weekly for two months and then once weekly for a month. The patient lies on the right side with hips elevated and is prepared by a saline cathartic at bedtime and a cleansing enema in the morning.

Oxygen—The intestinal oxygenation method of Felsen has been successfully employed by him (Golob (1936) and others, it is described under Ulcerative Colitis.

DIET, GENERAL AND NURSING CARE

In the severe cases, with fever and prostration, the patient must be in bed, of course, and should receive frequent feedings—every two and one-half hours, according to Reed—of boiled milk, stale or toasted white bread, white rice, soft cooked eggs, gelatin and tea. Adequate rest may be secured by use of one of the barbiturates (see Insomnia). If there is excessive frequency of bowel movements bismuth should be employed at once and paregoric may be given in 2-dmelm (8 Gm.) doses at two hour intervals to control colic. Occasionally it will be necessary to give a hypodermic injection of $\frac{1}{4}$ grain (0.008 Gm.) morphine sulfate, or $\frac{1}{32}$ grain (0.002 Gm.) dilaudid, with $\frac{1}{120}$ grain (0.0005 Gm.) atropine sulfate. Should a period of costiveness then succeed the diarrhea there is no harm in giving a cathartic. Tenesmus may accompany rectal ulceration, the following might be useful, as suggested by Fantus:

R. Iodoform	5iiss	10 0
Olive oil	3iv	120 0

Keep on ice. Inject 1 tablespoonful into rectum every four to six hours.

After the disappearance of acute symptoms in the fulminating cases there is no need to keep the patient in bed, indeed, in average cases without prostration or fever he need never have been put to bed—except during the period of emetine therapy, when experience dictates caution because of the cardio-toxic nature of the drug. In building up the diet one should bear in mind that this patient will require smoothness combined with high protein and low carbohydrate, many observers have also attested the value of richness in vitamins. The following will meet the daily requirement pretty well for average activity.

Breakfast

Cooked cereal with cream but *very little* sugar
 2 soft cooked eggs
 3 slices bacon
 1 or more slices toast or white bread with much butter
 Tea preferably for its astringency but coffee is permissible
 again little or no sugar

Luncheon and Dinner

Lean cooked meats generous portions
 Baked potatoes or rice much butter
 White bread and butter
 Milk as much as wished
 Gelatin dessert cream but no sugar
 Tea or coffee if habituated

Raw fruits had best not be allowed for quite a while but the strained juices may be taken unsweetened and in much moderation, no leafy or vegetable salads. Work sugar and green vegetables back into the diet very slowly. The studies of Faust and associates (1936) in dogs indicate great value for the oral (not parenteral) administration of liver as in pernicious anemia, convalescing trials in the human are still lacking. Rogers (1933) states that alcohol should not be taken by patients with amebiasis as it "strongly predisposes to amebic hepatitis and liver abscess." Hummel (1937) would also interdict tobacco.

A hint, probably well worth taking in chronically recurring cases, was recently given by Ghosh (1939), in India, who regulated the diet to maintain an alkaline reaction of the feces, instead of the acid reaction favored by *E. histolytica*, means to this end are the following: reduction in meat, rice, macaroni, cereals, bread, increase in fruit and vegetables, addition to the diet of figs, molasses and raisins.

While in general the chief propagator of the disease is not the acutely ill patient but the convalescent or chronic carrier of the cysts, it is nevertheless desirable to treat the excreta and bedclothes in the acute stage much as is done in typhoid fever, attendants must also look scrupulously to the cleanliness of their hands.

TREATMENT OF COMPLICATIONS

Abscesses of the lung and of the brain require the usual treatment for these conditions plus the systemic use of emetine. Peritonitis, perforation or severe bowel hemorrhage requires complete rest or immediate surgery, largely depending on the patient's condition. In liver abscess it is now generally agreed that emetine combined with aspiration is much preferable to surgical

drainage when there is no secondary infection, unless the symptoms demand immediate aspiration it is often well to give the emetine full chance, for if this is done the puncture can be avoided not infrequently. The other specific drugs, being at least potentially hepatotoxic, should not be employed in cases of known liver abscess until emetine, with or without aspiration, has brought about subsidence of the liver involvement.

TREATMENT OF THE CARRIER

In the treatment of the carrier we can only employ the remedies described for use in the acute sufferer from amebiasis.

PROPHYLAXIS

Dietary Precautions—Brief sojourners in the tropics where the incidence of amebiasis is highest should endeavor to eat only thoroughly cooked foods and drink only boiled water or bottled beverages which are known to have been sterilized. But this is difficult of accomplishment and of course does not afford protection against subsequent and extraneous contamination by food handlers and other carriers.

Purification of Drinking Water—When boiling is not feasible, purification of water may be accomplished by placing 19 drops of hypochlorite (chlorinated soda solution) in 1 pint (about 2 ordinary tumblerfuls) of water, letting it stand five minutes after stirring and then adding enough sodium thiosulfate (photographer's 'hypo') to overcome the disagreeable chlorine taste usually a crystal (or a very small pinch if in powdered form) of the 'hypo' will suffice. For purification of larger quantities, 1 teaspoonful of hypochlorite should be used per gallon of water.

Drug Prophylaxis—Of all the drugs diodoquin is best suited for prophylactic use. In Craig's (1940) opinion, he points out that its use is not accompanied by disagreeable symptoms even when given in large dosage over a long period. He advocates its trial in the following manner by those visiting infected country: 2 tablets of $3\frac{1}{2}$ grains (0.21 Gm.) after breakfast, 2 after luncheon, 3 after dinner—proportionate amounts for children. This dosage should be employed for twenty days even though the region is left before the expiration of that period; if the visit is longer than twenty days the course may be repeated after an interval of a week.

BACILLARY TYPE

Bacillary dysentery is an infectious disease caused by *Shigella dysenteriae* of which there are apparently four main strains—Shiga, Kruse, Flexner, Hiss and Sonne Duval—and very many related varieties. The cases range in severity from very mild to fulminating choleraic types; very many cases too are likely never recognized for what they are since this disease is a great mimic. In the average typical case the onset is sudden with rise in temperature, severe abdominal pain and tenesmus, early appearance of bloody and mucous diarrhea, and the symptoms of toxemia and dehydration. There is diffuse inflammation of the colon and lower part of the ileum with ultimately necrosis and extensive ulceration and very rarely perforation. Some of the cases become chronic. Adults between twenty and thirty and infants under two years of age are the most susceptible. The disease is endemic in the tropics.

but may become epidemic anywhere during periods of crowding, bad sanitation, privation and other causes not yet understood. Flies, contaminated food and water, and human carriers are the agents of its dissemination. It is now believed by many observers that most tropical dysentery is of the bacillary and not the amebic type, the asylum and prison dysenteries and some of the summer diarrheas in infants also belong in this group. Mortality varies widely with the locality and the particular outbreak, being from 2 to 80 per cent. Death is caused by toxemia, or later in the disease by peritonitis or inanition, heart failure or intercurrent pneumonia is frequently the cause during epidemics. Bacillary dysentery is notorious for the invalidism it causes.

THERAPY

Sulfonamides—The use of these drugs has completely altered the outlook in bacillary dysentery in recent years. Representative is the report of Lyon (1941) who studied 46 cases, the drug being used alternately in half the cases as they came, of each patient it was required that he have a history of acute onset with fever and diarrheal stools containing blood or pus, this onset not to have been more than seven days prior to admission, and that upon admission the rectal temperature was at least as high as 102° F (39° C), diagnosis was confirmed by stool culture when possible (i.e., in somewhat more than one third of both groups). In the untreated group of 23 patients the characteristic clinical course was pursued, but of the 23 patients treated with the drug 6 were not helped while 18 were strikingly benefited. Many of the recoveries were described as 'most dramatic in character' marked fall in temperature and leukocyte count and decided clinical improvement within twenty-four to forty-eight hours, early reduction in the number of stools and within forty-eight to seventy-two hours great improvement in their character as to blood, pus, or mucus content. Equally striking results have been reported by Ravenel and Smith (1941), and numerous others, marking an altered outlook toward this disease which can perhaps best be appreciated by practitioners in the South where bacillary dysentery has been a particularly severe scourge among the very young.

Sulfapyridine and Sulfathiazole—Sulfapyridine early proved to be the drug of choice in this malady but it has latterly been largely replaced by sulfathiazole which is equally effective and less toxic. Dosage is that employed in pneumonia (q.v.).

Sulfamylguanidine—This drug has been shown by Marshall *et al* (1941) to be very little absorbed into the blood stream but to exert a local action on the organisms in the intestinal tract. For children with bacillary dysentery the following dosage scheme has been recommended: initial dose by mouth 1½ grains (0.1 Gm.) per kilogram (2.2 lb.) body weight, succeeding doses of half this amount to be given every four hours until the number of stools per day is four or less, then the original full dose is to be given every eight hours for at least three days. It was this dosage which Lyon (1941) used so satisfactorily (see above) in his controlled study. For adults, Marshall *et al* recommend the same dosage except that when giving the drug every eight hours half instead of full doses per kilogram are to be used. Edwards (1942) says that sulfamylguanidine 'should rarely if ever be given continuously for longer than fourteen days'.

Sulfonamide Toxicity—See separate section on this subject at end of book

Cathartics—Prior to the advent of chemotherapy in this disease the attempt was made to lessen absorption and promote elimination of toxins by thoroughly washing out the bowel with cathartics and keeping it washed out, but this treatment is now surely outmoded since it is highly desirable that the sulfonamide remain in the tract

Adsorbents—Kaolin and charcoal were used before the introduction of the sulfonamides in the hope of adsorbing some of the toxins in which capacity it would seem that they were oftentimes quite effective kaolin up to 300 Gm in a pint of hot tea to be drunk during the day, charcoal preferably of animal origin because of its smaller particles, up to 80 Gm But the administration was always difficult and it is doubtful if they will any longer have a place in this therapy

Saline and Dextrose—It is of course of great importance to combat the dehydration and acidosis which occur with astonishing rapidity in fulminating cases, even though the sulfonamides are being administered Parenteral administration of dextrose in Locke's solution is the best way to accomplish this or in selected cases blood or plasma transfusion may be indicated

Relieving Pain—Though morphine or dilaudid may have to be administered in the beginning of severe cases colicky pain and tenesmus of average severity will be relieved by a few doses of some such prescription as the following

R) Codeine phosphate	3ss	2 0
Chloral hydrate	3v	20 0
Tincture belladonna	3v	20 0
Compound tincture cardamom to make	3iv	120 0
Label 1 teaspoonful every four hours		

Hot rectal irrigations are also used to combat tenesmus and the administration by mouth of 1 drachm (4 Gm) of bismuth subcarbonate at four hour intervals is said to be helpful Heat applied to the abdominal wall is recommended

Polyvalent Serum—Even before the advent of the sulfonamides it was the consensus that in mild cases likely to recover quickly the cost of the serum plus the probability of serum sickness contraindicated its use, while in severe cases it was by no means agreed by all authorities that serum treatment of the cases effectually lowered mortality, where used, however, it was advised that it be given early, intravenously and in an average dose of 200 cc for the adult It is extremely unlikely that serum treatment will hold any place at all in competition with chemotherapy

Convalescent Serum—Felsen (1940) advocates the intramuscular injection of 100 to 200 cc of pooled convalescent serum (adult dosage) within the first twenty four hours, or the transfusion, if compatible, of double these quantities of whole blood from a recovered donor He collects blood from convalescent acute cases at about the end of the third week

Vaccines and Bacteriophage—The value of these agents has not been proved

Diet—It is difficult to make any distinction between dietary treatment

of milk which apparently no matter how given, whether fresh diluted or disguised aggravates the colic beef or chicken broth must be substituted Strangely Corner (1935) with considerable experience in severe outbreaks states that occasional ice cream is well borne The excessive amount of butter in the amebic dysentery diet should be eliminated in severe cases of the bacillary form since fat is likely to increase this diarrhea Block and Tarnowski (1941) feel that bananas are a distinctly valuable supplement to the diet and Winters *et al* (1939) have had good success with pectin agar (see succeeding article on Infantile Diarrhea) There are also in existence some preliminary experimental data indicating that possibly a hitherto unsuspected type of vitamin deficiency underlies dysentery susceptibility but there is nothing as yet definitely applicable to man

Nursing Care—The patient must be kept as quiet as possible since the very frequent stools are terribly wearing even in the absence of toxemia To keep him warm will sometimes tax the ingenuity of nurse and physician Isolation and scrupulous attention to the personal hygiene of patient and attendants are fully as important here as in typhoid fever

Chronic Cases—Appendicostomy and washing out from above used to be much advocated but since it has been amply shown that the entire colon can be filled from below, I do not believe it is any longer a rational treatment Smyly says that cecostomy, with the opening of an artificial anus to give the colon complete rest for three months may prove a satisfactory treatment in exceptional cases Most patients respond to less heroic measures in a shorter time The silver salts are principally used locally an enema of 500 cc of a 1-100 argyrol (mild silver protein) solution or 1-500 protargol (strong silver protein) Copper sulfate is frequently used in 0.5 per cent strength or 2 per cent tannic acid solution recently the De Rivas technique of irrigating with copper sulfate solution, as in amebic infection has been favorably reported upon These solutions the silver salts especially stimulate an acute reaction and a reparative process but the balance between inflammation and repair is not always easy to strike they should therefore not be repeated too often Ten per cent silver nitrate rarely stronger may be applied directly to the rectal ulcers

INFANTILE DIARRHEA

In the good old days when privies were neatly whitewashed and there were still plenty of corner pumps and horses and flies and when the milkman drove about ringing his big bell in the heat of the day and ladling his wares from open cans into nicely sun warmed pitchers and jugs—in those far-off times a goodly proportion of infants quickly sickened and died in the late summer months of a condition known as cholera infantum Nowadays the scene is changed and 'summer diarrhea' as such has greatly diminished in the areas of modern civilization but nonetheless infantile diarrhea is still seen distressingly often throughout the year particularly in artificially fed infants and especially among the poor and less well nourished classes The etiology of these cases is complex some seem due to dietary errors doubtless many are really cases of bacillary dysentery, in some instances there is likely infection with a member of the *Salmonella* group or with a streptococcus or some other organism perhaps in a few instances the diarrhea is secondary to infection elsewhere Mortality is still very high

Apple (or Banana) Diet —In Germany some years ago there developed out of an old folk remedy the so-called "Moro Heisler apple diet" for the treatment of all sorts of diarrheal conditions in infants and young children, being especially effective in the type under present discussion. The enthusiasm of those who used this treatment indicated great satisfaction with it. Ripe, mealy eating apples cored and grated to a fine pulp (with or without previous paring) were given in quantities of 1 to 4 tablespoonfuls each hour during the day. If the acid flavor was objected to an inch of ripe mashed banana was added to each spoonful of apple. No other food was given. Patients take from 10 to 50 spoonfuls per day and it would seem that the more the better. Termination of the diet was made twelve hours after the appearance of formed or semiformed stools usually in twenty four, but perhaps thirty six or more, hours after beginning it. Mitchell (1935) used the following transitional diets for a few days in bringing the patient back to full feeding:

	<i>Infants</i>	<i>Children</i>
<i>Breakfast</i>	Cooked cereal (no milk) Apple pulp (4 tablespoonfuls)	Cereal (with skimmed milk sufficient to make edible) Toast Cocoa (made with water)
<i>Midmorning</i>	Apple pulp (1-4 tablespoonfuls)	Apple pulp Cracker (saline or soda cracker)
<i>Lunch</i>	Clear broth or bouillon Rice Junket (made from skimmed milk)	Broth or bouillon Rice Scraped beef or chicken Toast or cracker Junket (from skimmed milk)
<i>Midafternoon</i>	Gelatin	Gelatin and cracker
<i>Supper</i>	Cooked cereal Apple pulp	Cooked cereal Toast Cocoa Apple pulp or banana

Skimmed milk, whole milk junket, baked potato, custard, jam, marmalade and cream cheese may be added next. Cream is gradually returned to the milk, and meat, vegetables and fruits allowed in increasing amounts. Reappearance of diarrhea necessitates a brief return to the apple diet.

In recent years prepared apple powder has largely replaced fresh raw apple for this purpose. It is given in 4 to 10 per cent solution in water, weak tea or skimmed milk, 24 to 36 Gm. for infants under one year, 80 to 100 Gm. for older children. Many men have also been replacing apple with banana with good success, and latterly banana powder has more or less replaced the fresh fruit.

Pectin-agar —Malyoth having shown that pectin and cellulose are the two ingredients of apple likely responsible for its therapeutic effect, Winters and Tompkins (1936) introduced a pectin agar preparation for the treatment of these diarrheas. This seems adequately to replace apple or banana, fresh or powdered, and to be very simple to use. The ingredients of this preparation as described by Howard and Tompkins (1940), are pectin 6.3 per cent, agar 4.3 per cent, dextrinmaltose 89.4 per cent. One cup (8 ounces) of this powder yields 480 calories and serves well as a basic formula for the diets of nurslings and young children. For nurslings 8 ounces is cooked ten minutes

in a double boiler with 24 ounces of milk, poured into nursing bottles while still hot, when rewarmed and shaken it will feed easily through a nipple with enlarged opening. Since each ounce of this mixture contains 40 instead of the usual 20 calories it should be fed in only half the usual quantities fluid being administered otherwise. For children six months to two years 8 ounces of the powder is enoked with only 16 ounces of milk, or it may be cooked in a smaller amount of water and fruit juices added up to full volume. Flavoring agents such as vanilla chocolate, etc may be added, and the mixture may be frozen if preferred.

EPIDEMIC DIARRHEA OF THE NEWBORN

In recent years a number of epidemics of severe intestinal intoxication occurring as localized outbreaks among a hospital's population of newborn infants have been reported from several cities in the United States. Both sexes and all races are attacked but only during the first two or three weeks of life, older children and adults being apparently immune. The chief symptoms are the passage of numerous watery yellow stools without blood, mucus or pus; great distention, occasionally vomiting; marked dehydration; great and precipitous weight loss; possibly but not invariably fever, drowsiness, shock, and a very high mortality. The disease is extremely contagious but the etiologic agent has not yet been determined. In an outbreak in one of the Milwaukee hospitals in 1938 breast-fed infants either did not contract the disease or if they did so were able to survive the attack. In this epidemic acute enteritis was found in 87 per cent of the sixteen babies autopsied; with pneumonia the next most frequent finding though the latter predominated over all other findings in only three instances; in several instances there was aspiration pneumonia and in two of these it seemed to be the cause of death; as there was no evidence of an enteritis in these cases. However, in other epidemics elsewhere enteritis has not been always a predominating finding.

THERAPY

There is practically nothing to describe for these epidemics seem absolutely uncontrollable by the measures employed in bacillary dysentery and ordinary infantile diarrhea. In the Milwaukee outbreak (Cron, Shutter and Lahmann 1940) the sulfonamides were tried and failed but since the newer drugs of this series were not available at that time one may still hope for something from this type of chemotherapy. Transfusions from donors given a sulfonamide twenty-four hours previously, convalescent serum, autogenous vaccines all failed. It was thought that breast milk begun as soon as possible after a supply was obtained was helpful but the only babies who either escaped or survived the epidemic were those nursed upon human milk from the time of their birth. Lyon and Iolsom (1941), in an epidemic in Huntington, West Virginia felt that citrated whole blood (90 cc injected into the gluteal region) from a patient recently convalescent from clinical influenza was astonishingly helpful in 3 of their cases and they suggest the possibility that epidemic diarrhea of this type may be an expression of infection with influenza virus in the newborn.

It seems to be the consensus that to safeguard against outbreaks of this dreadful malady some means must be found for increasing the already pro-

digious efforts to attain asepsis in the maternity and newborn quarters in modern hospitals. The Milwaukee group is making a strenuous effort to increase the incidence of breast feeding as a precautionary measure of apparently proven value.

FLAGELLATE DYSENTERY

(*Giardiasis Lambliasis Balantidiasis*)

In recent years it has become generally recognized that infestation of the intestinal tract particularly of the duodenum and upper part of the ileum with the flagellate protozoan *Giardia (Lambia) intestinalis* is quite common throughout the world but whether this organism is often capable of giving rise to symptoms is still a moot point. Tropical physicians and parasitologists of experience are strongly opposed to the increasing tendency among non-tropical practitioners to assume without any basis in fact that these flagellates invade the gallbladder and higheriliary passages and give rise to a quite variegated array of symptoms. However some degree of possible pathogenicity is admitted even by the staunchest opponents of those who may be imagining more than they actually see. McGrath *et al* (1940) have reported a case of very severe infestation with the symptoms of idiopathic steatorrhea in which it was found at autopsy that the duodenum and upper part of the small intestine were denuded of lining epithelium and were dilated and the midportion of the ileum was extensively ulcerated and the lumen constricted, but of course it was not possible to show that these changes had been wrought by the giardial organisms. Anemia frequently associated with this infestation is admitted and a remittent type of diarrhea is granted by some observers the latter characterized by the frequent passage of liquid or semisolid stools of clay brown color and foul odor but only very rarely containing a little mucus or a tinge of blood. Similar if perhaps not entirely identical forms of this organism infest many domestic animals.

Balantidium coli a ciliated protozoan that is a common organism in the pig is capable of establishing itself in the colon of man and giving rise to symptoms much resembling those of amebic dysentery. There is extensive ulceration, invasion of the submucosal tissues and loss of considerable blood together with the passage of much shed necrotic epithelium in the diarrheal stools. Balantidiasis has been reported from many parts of the world but usually only a small group of cases in closely associated individuals or an isolated instance of the infection is described. Young (1939) reporting 7 cases of his own brings the number of cases reported in the United States to 39. Mackenzie and Bean (1938) believed that theirs was the first case reported in England.

THERAPY

Until recently in giardiasis the whole gamut of amebicidal and anthelmintic drugs has been run without much success but now it seems that a truly specific agent has been found in the synthetic antimalarial drug atabrine. Galli Valerio (1937) first reported its successful use in Switzerland and quickly thereafter confirmation came from practitioners in several other countries. Galli Valerio used the drug as in malaria i.e. 1 tablet of 0.1 Gm. (1½ grains) thrice daily for five days and so have most of the others who have reported. Tecon (1938) however thought that 1 tablet once daily for two or three

days was enough, but in the U S Navy, Love and Taylor (1940) feel that the larger course should be routinely employed since even it had to be repeated once after a short interval in order to rid one of their patients of all forms of the parasite, with the full course of 3 tablets daily for five days Kyser (1941) freed of parasites all but 1 of his 35 patients at the Mayo Clinic With this specific drug now available we should soon know whether or not *Giardia intestinalis* is a pathogenic organism

At the present writing the use of atabrine in balantidiasis has not been reported All the amebicidal drugs and the anthelmintics have failed to give consistent results precisely as in giardiasis, but in individual instances there are successes reported with several of them, for example, in the most recent American report, that of Young above referred to, carbarsone was satisfactorily used Mackenzie and Bean (see above) have made a wide departure in therapy by employing Loeffler's methylene blue because of its ability to stain the organism They had only one patient to treat but in her 2 retention enemas of the stain, given twenty four hours apart followed by a third two weeks later, seemed to clear the stools permanently of both ciliated and cystic forms of the organism Actually, however, these workers had been preceded by Chase and Tasker, who, in 1917, had used this stain both in enemas and by mouth, they used only the medicinally pure drug (methylthionin chloride), not that employed in staining because the latter contains traces of zinc, and gave 2 grains (0.12 Gm) every three hours by mouth and enemas of the 1:500 up to 1:200 aqueous solution (retained fifteen minutes) once or twice daily

STRONGYLOIDES DYSENTERY

(See the section on *Worms*)

EPHEMERAL FEVER

(*Febriculn*)

Certain fevers of one or at most three days' duration, unaccompanied by any demonstrable causative lesion, and disappearing as rapidly as they appear, have long been denoted "ephemeral" fevers for want of a better name Sometimes there is nausea, vomiting, colic, and perhaps chills It has been thought that exposure to sewage gas and foul odors from other sources is responsible for this type of fever, but it is extremely likely that as our diagnostic means and skill improve it will eventually be recognized that all these cases are abortive attacks of one of the clearly recognized infectious diseases

The fevers of unknown origin frequently seen in youngsters following a sudden change of environment probably belong in this category

THERAPY

Nothing, of course, has been evolved beyond the usual palliative measures designed to ease such slight symptoms as are met with here

EPIDEMIC ENCEPHALITIS

(*Encephalitis Lethargica, St. Louis Encephalitis, Japanese Type B Encephalitis, Australian X Disease, Equine Encephalomyelitis, Toxoplasmic Encephalitis, Russian Encephalitis, Sporadic Encephalitis of Unknown Origin*)

Encephalitis lethargica first appeared as an apparently new disease on the Continent in 1915 and for a few years thereafter was epidemic throughout the western world. Many investigators believe this outbreak to have been identical with the "nona" of the 1890's and indeed many earlier visitations the earliest of which perhaps was that described by Sydenham as having prevailed in London in 1673 to 1675. Since 1926 only an occasional sporadic case has been seen. It was thought that this disease was caused by a filtrable virus, perhaps related but not identical with those of herpes and influenza, but this fact was never established. The acute clinical manifestations were very complex and appeared either suddenly (often after a period of enforced activity) or gradually, often, but by no means invariably, there were the following symptoms: increasing drowsiness, slight fever, diplopia or other eye muscle disturbances, salivation and head cold. After the patient took to bed he usually lay relaxed and absolutely quiet, with one or both lids ptosed, apparently but not actually asleep, indeed, insomnia was of frequent occurrence despite the mask of deep stupor. Other patients manifested evidences of motor irritation from the beginning: movements of the pill rolling, Parkinson type, or they were choreoid, or clonic spasmodic. Mentality was usually impaired especially as to memory, attention, and orientation. Emotional disturbances were common, and in some cases marked alterations of character and oddities of behavior were outstanding features. Delirium sometimes alternated with periods of stupor. In many cases there was an increase in globulin and sugar and a slight increase in the cell count in the spinal fluid. The disease occurred in the winter and spring and affected principally individuals in the third and fourth decades, the mortality was between 25 and 40 per cent. Convalescence was very slow and the sequelae, from which recovery was also very slow if it occurred at all, were much dreaded: persistent insomnia or prolonged somnolence, Parkinson-like syndromes, autonomic pupillary, respiratory, cardiac, sphincter, etc., disturbances, mental impairment, psychoneurotic manifestations, etc.

The newer types of encephalitis differ markedly from the above. St. Louis encephalitis appeared in several counties in Missouri in 1933 and recurred in that area in 1937. In the first epidemic there were 1097 cases with a mortality of about 20 per cent, the second time the mortality was 24.8 per cent with only 431 cases, most of the deaths in both epidemics occurring in elderly people. A few other outbreaks of somewhat smaller proportions have occurred in other areas of the United States. St. Louis encephalitis occurs only in the summer and affects individuals of all ages but principally in the upper age groups. The attack usually begins with chilliness and malaise, vomiting and often severe abdominal pain, sometimes quite high fever and often a disproportionately slow pulse, grippe-like aches and pains, and early signs of cerebral involvement: severe headache and stiff neck, mental confusion and perhaps even delirium, convulsions or coma, tremors and a variegated lot of other neurological signs, but notably absent or at most only transiently

present are the ocular manifestations characteristic of encephalitis lethargica. Globulin pressure and the cell count (predominantly lymphocytes) are usually moderately increased in the spinal fluid but the sugar remains normal in most instances. The course may be very stormy but recovery is usually complete in two or three weeks and mild subjective nervous complaints are the most common residuals (as revealed in the Bredeck *et al* [1938] follow up study of the first epidemic in St. Louis). It is believed that many subclinical cases occur during an epidemic. A number of quite similar outbreaks have been reported from Japan but the mortality there seems to run as high as 50 to 60 per cent.

A filtrable virus has been recovered in both St. Louis and Japanese encephalitis, been cultured and established in several experimental animals, but it appears that the two viruses are distinct or at least distinctive strains of the same virus. There are several epidemiologic features of these outbreaks which strongly indicate that there is an insect vector, but it has not yet been identified. The "X" disease occurring in Australia in 1917 and 1918 was apparently similar to the St. Louis and Japanese types, but nearly half the cases occurred in children under five years of age.

Equine encephalomyelitis is a very recently recognized disease in man though it has been known in horses for a long time. The first outbreak in the human was reported in 1933, first from the New England and then from the Western States. The disease occurs in summer and is clinically very similar to St. Louis encephalitis except that it attacks children mostly, is usually abrupt in its onset and sharp and short in its course, the mortality is very high (70 per cent), and such permanent residuals as paralysis and mental changes are common. Equine encephalomyelitis has been shown to be due to a filtrable virus recoverable from both horses and man but the Eastern and Western strains are different, there is also a distinctive Venezuelan strain. Investigation is now revealing that perhaps the horse as well as man is only more or less accidentally invaded and that the true and natural host is probably that great horde of birds that annually migrates up and down the land, the disease is experimentally conveyed also to domestic fowl and to many animals both domestic and wild. So far five mosquitoes and the common woodtick have been convicted as vectors of animal infections but as yet no human case has been proved to have been caused by the bite of one of these insects. In Far Eastern Russia, where a disease described as similar to St. Louis and Japanese encephalitis prevails, a woodtick is said to have been convicted as the vector to man—I imagine that this encephalitis is really more closely akin to our equine encephalomyelitis for rodent hosts have already been found.

Just about as I write, a toxoplasmic encephalitis has been described but the information regarding it is still quite meager. And finally, to complete the list of types of epidemic infectious encephalitis, it should be mentioned that sporadic cases of encephalitis are being reported which do not, immunologically at least, fit into the description of any of the above-listed entities.

THErapy

The description of therapy in this group of diseases will require little space, since there are no specific remedial agents and only symptomatic treatment is available. During the acute stage, light but ample feeding, the forcing of

fluids, the keeping of the body clean, and the protection of the patient from all annoying sensory stimuli, and in some instances the use of salicylates to relieve pain, are indicated. In the treatment of the insomnia or the excited states, of course, resort must be had to full doses of sedatives (see *Insomnia*), but it is possibly advisable in choosing among the barbiturates to omit phenobarbital for the Ziskinds (1937) found that this drug aggravates rigidity in established parkinsonism. During the first St. Louis epidemic (Eschenbrenner, 1931) patients admitted to the Isolation Hospital were given spinal puncture on admission and it was repeated when there recurred evidences of increased pressure or meningeal irritation (Slesinger, 1936, found the routine initial puncture of no advantage). Ten per cent dextrose solution was routinely given intravenously, daily during the severe stage—750 cc. to adults and correspondingly smaller doses to children. Those with severe signs of cerebral edema were given 50 cc. of 50 per cent dextrose solution intravenously every twelve to twenty four hours, efficaciously in most cases. Gareau (1941) used this treatment frequently also in his cases of the equine type. Drastic saline purges were used in some instances in the effort to reduce the edema further. Retention of urine in the women and older men sometimes required several catheterizations or the use of the retention catheter for several days. Hyperpyrexia frequent in the acute cases, yielded to tepid baths, alcohol rubs and the ice-bag to the head. Delirium tremens responded to large doses of paraldehyde.

The sulfonamides have been tried in numerous instances and have always failed, as indeed was more or less predictable since neither in experimental nor spontaneous virus infections have they ever succeeded with the possible exception of trachoma. Most men see no reason to expect anything from convalescent serum, but Slesinger felt that it was of some value in the 22 cases of the St. Louis type in which he tried it.

In the more stuporous patients nasal tube feeding must be resorted to. Barthorka's formula (P, 70, C, 105, F, 160, Cal, 2500, fluid, 1760 cc.) follows

Mix together and boil

1000 cc. milk 300 cc. cream

3 eggs 3 egg whites

120 cc. sugar or lactose

Cool and add the following

100 cc. orange juice 15 cc. cod liver oil

3 teaspoonfuls brewers' yeast

Strain through a very fine sieve. Serve at body temperature 150 to 200 cc. every two hours

The treatment of the psychoneurotic sequelae, which characterize most notably encephalitis of the lethargic type, being largely systematic attempts at rehabilitation, cannot be described here. Arsenic, iodides, and indeed practically all the other specifics and near-specifics have been tried as aids to this process, and found wanting. To control parkinsonism (muscular rigidity, tremor, drooling, upward rolling of the eyes), drugs of the belladonna series are used, and some other agents also.

(a) Atropine sulfate is started at 1/80 grain (0.75 mg.) thrice daily and increased by 1/120 grain (0.5 mg.) twice daily until maximal therapeutic effects, or toxic disturbances, are obtained. In some instances doses of $\frac{1}{4}$ to

$\frac{1}{2}$ grain (10-20 mg) daily are given for many months, this was the average optimal, indeed, in Hall's (1937) series, and in one of his cases 54 mg was required and tolerated Jewett *et al* (1933) have also used high dosage satisfactorily Schlezinger and Alpers (1941) have used a synthetic atropine like drug syntropan and thought it of definite value, maximum benefit was experienced when the total daily dosage of 2.4 Gm could be tolerated

(b) Bulgarian belladonna for some years there has been an impression on the Continent that a white wine decoction of Bulgarian belladonna was superior for this purpose to atropine In England the findings of Hill (1938) and of Alcock and Carmichael (1938) have been conflicting In the United States Neal and Dillenberg (1940), making trial of the decoction under the auspices of the Matheson Commission for Encephalitis Research in New York City, obtained results in approximately 100 patients which they described as far superior to those obtained with any other form of symptomatic treatment The decoction having been found to deteriorate upon standing, a tablet has been prepared and is available under the name 'bellahulgara' It was found necessary to use sufficient dosage (which must be separately determined in each patient) to cause marked dryness of the throat and blurring of vision and then when these symptoms subside after a few days on this dose, to push up to the point of causing really toxic symptoms, such as gastrointestinal and urinary disturbances, headache and dizziness Fabing and Zeligs (1941) have found a white wine extract of USP belladonna root fully as effective as the Bulgarian preparation, the point seems to be that white wine extracts yield products qualitatively different from those obtained by hydroalcoholic extraction (tinctures)—if they do, I think some time must pass before we can be sure of this

(c) Scopolamine hydrobromide (hyoscine), 1/200 to 1/100 grain (0.0003-0.0006 Gm) several times daily

(d) Stramonium the powdered leaves (in capsules or pills) are given at one or two hour intervals until good effect is obtained, after which a maintenance dose is employed In the beginning 15 to 30 grains (1-2 Gm) may be distributed during the twenty four hours, a maintenance dose of 8 grains (0.5 Gm) has been found to be well tolerated for many months Of the tincture 60 to 90 minims (4-6 cc) three times daily is generally effective

Hurst (1934) has found that he can continue the use of a drug of the above group in some patients after there is complaint of dryness of the mouth and paralysis of accommodation by combining with it 1/10 grain (0.006 Gm) pilocarpine nitrate, some of his patients receive doses as large as $\frac{3}{4}$ grain (0.024 Gm) Solomon *et al* (1937) found benzedrine sulfate of some adjuvant value especially when symptoms of drowsiness and lack of energy predominate, Finkelman and Shapiro (1937), Matthews (1938) and Davis and Stewart (1938) had similar experiences

Laugel Lavastine and Sterne (1932), in France, have used trypan blue in 1 per cent aqueous solution, 1-cc injections intravenously at two-day intervals, followed by 4 injections of 2 cc each at similar intervals, a month is allowed between courses There is usually a slight nitritoid type of reaction but no serious toxic effects A bluish tinge to conjunctiva and skin indicates the stopping point of the whole treatment They reported quite satisfactory results but McCartan (1934) was unable to duplicate the findings in England Acriflavine has been similarly recommended though more particularly for

use in acute cases, but the Matheson Commission, in 1932, thought that the recommendations were based "upon opinions rather than results."

The present vogue for fever therapy has caused some enthusiasts to cock an eager eye at this syndrome but no careful clinical study has been published as yet. Riesman (1935) cautioned and Ornsteen (1936) agreed that such treatment may even do harm. It has been alleged that vitamin B₆ (pyroxidine hydrochloride) is effective, but Zeligs (1941) failed to confirm this impression in a group of 15 patients to whom repeated intravenous injections of 50 to 100 mg. were given, Barker *et al.* (1941) also failed in their 7 patients.

PROPHYLAXIS

Slesinger (1936), in the outbreak of St. Louis type encephalitis in Windber, Pa., felt that convalescent serum was definitely worth employing in prophylaxis but this impression seems to have been based solely upon the fact that 2 cases occurred in the exposed hospital personnel prior to the administration of 5 cc. of the serum to 7 of the remaining personnel with the occurrence of no new cases thereafter.

A vaccine of definitely protective value against equine encephalomyelitis has been developed and extensively employed in horses and mules. Beard *et al.* (1941) have used it experimentally in man and find it protective at least so far as development of satisfactory antibody titer is concerned. It has not yet been tried during an epidemic and indeed Hammon (1942) feels that such trial is not yet practicable or advisable.

EPIDEMIC PLEURODYNIA

(Devil's Grip, Epidemic Myalgia, Bornholm Disease, Bamle Disease)

Epidemic pleurodynia is an acute infectious disease characterized by sudden onset with excruciating muscular pain at the site of the attachment of the diaphragm to the anterior thoracic wall on either side, or in the epigastrium, marked increase in rate and decrease in amplitude of respirations, several degrees of fever and rather constant headache, but rarely pain elsewhere. The aching muscles are sometimes tender and noticeably swollen. The pain usually leaves within twenty-four hours as suddenly as it came, the fever also subsides, the patient breaks out into a sweat and being greatly relieved, falls into a refreshing sleep. There is often an attack of lessened severity one or two days to a week later, but a third seizure is rare. Muscular tenderness and swelling often persist for several weeks after subsidence of the acute attack. Howard (1938) notes that in some instances defecation is more or less frustrated for a time by the excruciating pain. Children seem to be more susceptible to the disease than adults.

Rimpau (1938) claims that this entity was first described by the Dane, Hannaeus, in 1735, and all students of the subject agree that it was observed in Iceland in 1856 and again in 1863, then in Norway in 1872. Its first appearance in America was apparently in 1883, at which time Dabney described it without knowledge of Finsen's prior notations on the Scandinavian cases.

Since then outbreaks have been recorded in England (where Pickles' graphic accounts show how puzzling the attacks may be unless this entity is borne in mind), Denmark (Sylvest's monograph, now available in English, is very excellent), Sweden, Finland, Germany, Portugal, New Zealand, Switzerland and numerous parts of the United States. The most recent bacteriologic studies, those of MacDonald *et al* (1937), have revealed nothing regarding the etiologic agent. Small has found a plasmodium in the blood but no one else has succeeded in doing so. Since this is a summer disease and often attacks several members of a family at about the same time, it has been looked upon as atypical dengue or at any rate mosquito borne, but these surmises remain uncorroborated. It is likely that the disease spreads by direct contact but nothing more exact than this is known with regard to its epidemiology.

THERAPY

The patient wishes to lie undisturbed, as every movement of the trunk causes an agonizing twinge of pain. In a few cases, hot or cold applications are a sufficient analgesic measure, but usually some drug has to be used in addition. Acetanilid, 3 grains (0.18 Gm), acetphenetidin (phenacetin), 5 grains (0.3 Gm), antipyrine (phenazone, B.P.), 5 grains (0.3 Gm), acetyl salicylic acid (aspirin), 10 grains (0.6 Gm), have all been used at three to four hour intervals. In the more severe cases these drugs are not at all effective and opiates must be resorted to, but before giving morphine or dilaudid one might try a few doses of the following combination, cutting the amounts in half for children under fifteen years.

R) Codeine phosphate		
Phenobarbital		
Extract hyoscyamus	℥ gr vj	0.4
Acetanilid	gr xxvj	0.0
Divide into 12 capsules		
Label 1 capsule every three hours		

Small states that the prompt exhibition of quinine sulfate, in doses of 3 to 5 grains (0.18-0.3 Gm) every two hours until 20 to 30 grains (1.2-1.8 Gm) have been given appears to terminate the disease specifically and to prevent the recurrence of paroxysms. He directs that half this daily dosage should be maintained for a period of one week after the temperature has become normal. I have found no other record of this felicitous use of the drug.

EPIDEMIC SORE THROAT

(Septic Sore Throat, 'Glandular Fever')

This is the type of sore throat which appears in the winter and spring in explosive epidemics and is in most instances directly traceable to the ingestion of milk, or milk products which are contaminated with *Streptococcus epidemicus*. The symptoms in the individual are sudden onset of chilliness, malaise, headache and vague body pains, high rise of temperature and

swelling of the cervical lymphatic glands. The pharynx is extremely painful, swollen, congested, and usually shows a diffuse, thin grayish exudate, in some instances (Tilley and McKenzie, 1935) the larynx is chiefly affected. The most frequent complications (in from 2 to 6 per cent of cases) are glandular suppuration, otitis media, peritonsillar abscess and arthritis. In some cases a scarlatiniform rash appears, indeed, it is nowadays accepted by most observers that streptococcal sore throat and full blown scarlet fever are very closely related entities. The mortality in some epidemics has been as high as 3 per cent. In most cases the symptoms subside in a few days, but the patient remains prostrated for some time longer. A recurrence several days after resuming activity is not uncommon.

THERAPY

Gallagher's (1937) use of sulfanilamide did not indicate that it had any marked effect upon the outbreak except that if given early it seemed to shorten the time during which throat cultures remained positive, but it seems to be the general opinion now that much better results than this are being obtained. Most attempts at specific therapy with antistreptococcal sera or vaccines have failed, but Camps and Wood (1936) in a British epidemic of about 1600 cases felt that the intramuscular injection of scarlatinal antitoxin many times shortened the course and lessened the complications and that complicating arthritis was definitely improved by it. Dobell's solution (Compound Solution of Sodium Borate, N F) diluted one half with water, or Alkaline Aromatic Solution, N F (which much resembles the nostrum "glycothymoline," so beloved of the lay public—and the profession?) is usually very gratefully received by the patient when used as a spray. Cold packs about the throat often give much relief. Otherwise the symptomatic handling of these cases does not differ markedly from that of influenza, discussed elsewhere in this book, see also Scarlet Fever. Suppurative complications in the neck require surgical treatment.

ERYSIPELAS

Erysipelas is an acute disease characterized by a spreading erythematous skin lesion plus more or less profound constitutional symptoms. It is known to be caused by several strains of the hemolytic streptococcus, perhaps but not certainly that particular one known as *Streptococcus erysipelas*, the organism is thought by some to enter a preexisting skin abrasion in all instances though history of antecedent injury is not obtainable in most cases. Mucous membrane cases are rare. Active adults in the middle decades, persons who have recently undergone a major operation, and women in the puerperium are the most frequent victims though individuals of any age and either sex are liable to the disease. Some persons manifest an especial susceptibility (perhaps because of some nasal or other focus of infection or because the skin remains hypersensitive to the organism) and have many attacks during their lives. The face is more often affected than

any other portion of the body. Mortality seems to range between 10 and 20 per cent in adults but is much higher in infants and in the aged.

The onset is sudden with high rise of temperature, malaise, headache, sometimes vomiting, and not infrequently delirium. The skin lesion appears coincidentally with the constitutional symptoms. The typical lesion is a red, swollen area with sharply demarcated and elevated border, small, flame-like extensions along the lymphatic channels are usually seen beyond this border. There is often a scattering of small vesicles throughout the affected area. The lesion spreads rapidly, and as it extends the earlier affected portions subside and desquamate. Sometimes localized abscesses, or necrotizing ulcers from secondary infection, form in the border, or the whole region may be undermined with pus. Pain, often quite severe, is of the burning order. The swelling in typical cases is very considerable. Fever usually persists for two or three days and then falls by lysis or crisis, usually several days before the complete subsidence of the skin symptoms. However, one cannot make any definite prediction in regard to the course of the fever, and indeed the whole clinical picture may persist, with relapse after relapse for several weeks instead of the usual duration of four to eight days.

This disease, though contagious and serious enough, does not tend to become epidemic and has not been given great attention by medical writers through the ages. Hippocrates did not describe it, though Galen mistakenly accepted his account of anthrax as applying to erysipelas. It is extremely likely that some of the cases of ergotism, which were so numerous during the Middle Ages, were really this disease. Tehleisea showed the streptococcus to be causative in 1883, Tunnichiff definitely separated the streptococci of scarlet fever and erysipelas in the period 1920 to 1927.

THERAPY

Sulfonamides—There can be no doubt that the drugs of this group have supplanted every other agent as the method of choice. There are numerous careful studies available of which the following are characteristic. Hoyae *et al* (1939) have reduced erysipelas mortality in Cook County Hospital to 2.46 per cent including all types and age groups and even deaths which occurred shortly after admission. Nelson *et al* (1939) compare the results at Bellevue Hospital, as follows: in 406 patients treated with erysipelas antitoxin the mortality for adults was 9.2 per cent, for children 37.5, in the group of 344 sulfonamide treated cases these figures were respectively 1.5 and 12.9 per cent. Snodgrass *et al* (1938), in England report a total mortality rate of only 2.06 per cent in 242 patients. Typical is the experience of Foley and Yasuna (1940), in Boston, who report that in their 80 sulfonamide treated patients a return to normal temperature was had almost two days earlier than in the 80 control cases; the hospital stay was shortened three days; complications occurred only half as frequently. The lesion ceases to spread within forty-eight hours in the experience of most observers but begins to change its appearance in half this time, in no instance in the 163 consecutive cases of Shank *et al* (1941) did the lesion continue to spread after thirty-six hours on chemotherapy. See Sepsis for details of therapy.

Ultraviolet Irradiation—The studies of Ude and Platou (1930) and of Titus (1933) introduced the American and British worlds to ultraviolet irradiation in erysipelas which had been having good reports on the Continent

for about ten years previously. Comparative series of cases showed the method to be very likely more effective than serum therapy. Lavender and Goldman (1935), equally with Titus stressed the need for boldness in dosage: their patients received an average of 3 exposures twenty four hours apart, of about 18.8 erythema doses per exposure. The involved area and the region 1 to 2 inches surrounding it are treated. In infants Nightingale and Starr (1934) gave 3 exposures of 1.5 erythema doses on successive days regardless of the clinical course. Willis (1939) has recently given 3 daily exposures of 6 erythema doses with the light at 10 inches and making no allowance for infants or blondes.

It is very likely that ultraviolet light irradiation will settle down into second place to sulfonamides as method of choice.

Antitoxin (Serum) Therapy—After its introduction by Birkhaug in 1926 and original extensive trial at Bellevue Hospital, the specific erysipelas anti-streptococcic serum was widely used and seemed to justify the early hopes that were felt for it. It is expensive, however, and carries with it the threat of serum sickness and immediate or delayed reaction to horse serum which makes precarious the position of any serum that does not give almost perfect results. Fox (1937), analyzing his 378 cases found that mild and moderate clinical types responded well to any of the empirical measures and therefore felt that serum should be employed only in severe cases. Symmers and Lewis of Bellevue Hospital recommended the introduction intramuscularly of 20 cc at the moment of the patient's admission repeating usually at intervals of twenty four hours until the erysipelatous blush disappeared, the edema was dissipated and the temperature became normal. Often 2 or 3 injections were necessary, occasionally more. In infants the dose was 10 cc.

That serum therapy will hold any place for itself in competition with the sulfonamides is extremely doubtful. Toomey (1938) very trenchantly made this point in effect when he reported a total mortality rate of 13 per cent in his large series of serum treated cases as against 15.5 in the untreated cases and pointed out that it is not necessary to use a control series to point out the benefits of antitoxin in diphtheria and of the sulfonamides in erysipelas.

Miscellaneous General Measures—Types of therapy which formerly had their advocates and have now been practically abandoned in favor of the sulfonamides are convalescent serum, blood transfusion, foreign protein therapy, tincture of ferric chloride.

Local Measures—The application of cold compresses is often soothing. Sometimes the making of the compress with saturated solution of magnesium sulfate instead of plain water, affords relief from the burning pain but this treatment apparently enhances the development of abscesses. Hallay powders the diseased area with sodium bicarbonate. From 10 to 20 per cent of ichthyol in an ointment in some cases exerts an analgesic effect. Hydrous wool fat (lanolin) should be used as a base because its adhesiveness permits of long application. Fox (1937) prefers continuous wet compresses with 1:1000 Burow's solution to all other local applications. Painting the skin beyond the border of the lesion with tincture of iodine, or a strong solution of silver nitrate, is said sometimes to stop the advance of the process. Eldridge applied a .5 per cent aqueous solution of mercurochrome to the whole affected area once daily until the eruption was well on its way toward subsidence, Adams

has used brilliant green. Some men experienced in the handling of many cases of erysipelas object to a number of the above measures because they obscure the true appearance of the lesion. Ainta and Woodyatt introduced the practice of circumscribing the diseased area with a stripe of nonflexible collodion $\frac{1}{2}$ inch wide and $\frac{1}{2}$ to 1 inch in advance of the line of induration. As it dries the stripe is painted over repeatedly to make a deeply constricted and unbroken furrow. Very good results are sometimes reported with this method, but nowadays the sulfonamides effect such early changes in the lesions that this method of attack is only rarely employed.

Prevention of Recurrent Attacks—As a result of the investigations of Amoss, one of the pharmaceutical manufacturing houses has made available extracts of 7 strains of streptococci for use in skin testing to determine by allergic reaction which should be used for desensitization in the individual case. The area of previous involvement and a corresponding area on the other side of the body are injected intracutaneously with 0.05 cc. The previously involved area usually shows more marked reaction to one of the strains and this one is then selected for the desensitization attempt, beginning with 0.1 cc. increasing doses are injected at five-day intervals until 1 cc. is given. After 6 of the 1-cc. doses skin tests are repeated to determine the state of susceptibility. Amoss (1931-1936) stated that in 38 cases thus treated he has stopped the attacks but that in 2 there were recurrences after long intervals, 1 at eight and 1 at nine years after desensitization. The injections were repeated and no further attacks occurred. I have seen no recent reports of the employment of this method.

ERYSIPELOID

Erysipeloid is a disease which has been shown to be caused by a modified form of the *Erysipelothrix rhusiopathiae* of swine erysipelas, a bacillus that is apparently either pathogenic or saprophytic throughout the animal kingdom. In America most of the cases have been reported from the Atlantic seaboard, with a few from the Great Lakes region, and have nearly all been in fish handlers and in handlers of the flesh of swine in packing houses. But the exceptions exhibit a wide gamut of possibilities, such as injury of the hand in the bed of a dried creek, skinning a rabbit carrying an opossum by the tail. Lawson and Stinnett (1939) had under observation 210 cases which occurred within one year in a factory making buttons from cattle bones, and Gross (1940) reported 13 cases among veterinary students with horse cadavers established as at least one source of infection. The disease is characterized by early pain followed by the appearance after an incubation period of two to four days of a sharply circumscribed quadrangular bluish-red lesion on the skin at the site of the infecting injury, the inflammation often gradually spreading to involve a large part of the hand. Sometimes it clears up in one finger but goes down another and may then even return to the site originally infected. There is local pain and swelling but the latter rarely extends above the wrist. Constitutional symptoms are mild, but cellulitis,

lymphangitis, and lymphadenopathy may occur, and the appearance of a diffuse erythema accompanied by the symptoms of sepsis has been reported. The majority of cases run a self limited course of about three weeks but in Germany, and recently in America (Klauder, 1938), there has been observed a chronic form of the disease which is characterized by polyarthritis, indeed, in America some of the cases have been observed to start up again in previously uninvolved areas after a short period of apparent cure. Russell and Lamb (1940) have reported bacterial endocarditis caused by *Erysipelothrix rhusiopathiae* as a fatal complication in one case, such observations had previously been made in Germany.

THERAPY

The only distinctive treatment which has been developed consists in the preliminary trials of a specific antiserum. Callomon in Germany, recommends the injection of 10 to 20 cc of this serum subcutaneously in the affected arm and describes good results both when using it in treatment and as a prophylactic measure immediately after the accidental inoculation. In America Klauder and Harkins (1931), and Ritchie and Becker (1931) induced healing of the lesions in about five days following a single injection of 25 cc into the gluteal region. However, the incidence of serum sickness has been particularly high after the systemic use of this serum. In Klauder's (1938) latest report he states his belief that the serum is indicated only if the infection persists for a month, if it progresses rapidly, or if arthritic symptoms are conspicuous. He then gives 100 to 150 cc (provided there is a negative reaction to cutaneous testing) intramuscularly in the course of a few days, some of this being injected locally. Locally, from 0.25 to 0.5 cc is introduced into numerous areas about the advancing border. A local reaction usually follows these injections swelling pain in the joints of the involved hand, urticaria near the site, and sometimes tenderness and enlargement of the lymph nodes draining the site.

Of course a wide variety of locally applied treatments have been tried. Klauder feels that splinting the hand is to be preferred to the use of a sling and favors the application of constant wet dressings of 12 per cent ichthammol (ichthyol) in alcohol. He further thinks that repeated erythema doses of ultraviolet light may be helpful but admits difficulty in evaluating treatment since the infection usually apparently runs a self limited course.

FOOT-AND-MOUTH DISEASE

Foot and mouth disease is a highly contagious malady of domestic hoofed animals, a few cases have also been seen among wild rats, and cats hedgehogs and perhaps other rodents can be experimentally infected. It is caused by a filtrable virus which is sometimes transmitted to man through the medium of infected milk or milk products or contact with diseased animals. The human cases are rare and transmission from man to man doubtful. Among livestock the disease is widespread in Europe South America and other parts

of the world, the United States has several times been threatened with serious epidemics, which have been stamped out by mass killing, immediate burial, and rigid quarantine. Studies in England have shown that dressed carcasses of infected animals may retain their infectivity even after ten weeks of refrigeration.

That great man, Girolamo Fracastoro (1484-1553)—who wrote the first complete description of syphilis, foresaw clearly the modern conception of the bacterial causation of disease and performed many other feats of original genius—described the first recorded epidemic of foot and mouth disease. And, indeed, since his time there has not been a great deal written upon it in the strictly medical press. In 1898, Loeffler and Rosch proved experimentally that the malady is caused by a filtrable virus. I give Clough's summary of the symptoms: 'A mild febrile infectious disease, characterized by the appearance of an erythema and a superficial vesicular eruption over the mucous membrane of the mouth and on the skin of the hands and feet, by salivation, by swelling, burning and paresthesia of the affected parts with subsequent desquamation, and by healing of the ulcers without scar formation.' Wagener (1938) says that etiologic diagnosis is obtainable by inoculating blister fluid into the scarified skin of a guinea pig's foot.

THERAPY

Treatment consists in the use of antiseptic mouth washes such as 1:2000 potassium permanganate. The silver nitrate stick may be applied to the ulcers just as in the treatment of canker sores. I imagine the lotion of calamine and zinc (see Index) would be soothing when applied to the lesions on the body surface, and an ointment containing about 0.5 per cent holocaine (phenacaine) would allay mucous membrane pain. Very little has been written about the treatment of the disease, all attempts to influence its course by the intravenous introduction of dyes or other antiseptic substances have usually not succeeded, but von Scheitz (1934) has stressed the beneficial effects of neoparsphenamine.

GANGOSA

(See *Fars*)

GAS GANGRENE

(See *Sepsis*)

GERMAN MEASLES

(See *Measles and German Measles*)

GLANDERS

(Farcy, Malleus)

Glanders is an infectious disease of horses and mules. It is caused by *Loefflerella mallei*, and is communicable to man. The cases in man, which are fortunately rare for the disease is usually fatal, are nearly all contracted directly from a diseased animal, though the danger of laboratory infection with the organism is very great, as was dolefully reemphasized in Prague, in 1924, when 3 well known scientists succumbed to the disease within a brief period. The outbreak which they were investigating claimed in all 7 deaths (in 7 cases), all deriving from one infected horse. Acute glanders in man may begin with symptoms indicative of almost any of the other infectious diseases, which makes early diagnosis very difficult, however, Symmers says 'The occurrence of symptoms of an acute infective disease in an individual who comes in contact with horses and who presents multiple abscesses in the skin or in the mucous membrane of the nose, with deep seated pain or tenderness, indicative of abscesses in muscle tissues, tendon sheaths fascia or periosteum, with or without joint symptoms should suggest the diagnosis of glanders in spite of the extreme rarity of the disease, and confirmation should be sought in isolation of the causative bacillus and guinea pig inoculation.' There is also a chronic form of the disease which must be differentiated (Burgess, 1930) from granuloma inguinale, lymphogranuloma inguinale, tuberculosis of the skin, syphilis and mycotic and yeast infections.

It is thought that the strange affliction of animals and men during the ninth to twelfth centuries, called *malum malannum* because of its recurrence in troublous years, was either anthrax or glanders. Solleysel described the transmission of the disease from horse to horse in 1664. The classical monograph on the disease in man is that of Rayer, in 1837. Loeffler discovered the causative organism in 1882.

THERAPY

There is no specific treatment for glanders in man. The palliative measures directed to the relief of the general constitutional symptoms do not merit special description here. They are such as are applied in any other fulminating condition. It is said to be advisable to excise the local nodule where possible, though in an outbreak, in 1926, of 7 cases in eastern Austria, 5 terminated fatally in spite of the fact that the original focus was eliminated in each case. A grave disease, then, for which we have no remedy.

INFECTIOUS MONONUCLEOSIS

(Glandular Fever)

This is an infectious and probably contagious disease characterized by intermittent or remittent fever which continues for one to three or four weeks. Complaints of general malaise, sweats, sore throat, general enlargement of the superficial lymph nodes (suppuration very rarely occurs and salivary gland involvement is rare also), frequently a palpable spleen, perhaps a rash,

and a mononuclear leukocytosis which closely resembles that of acute leukemia without the anemia and usually without the platelet reduction characteristic of the latter. Some cases with visceral glandular enlargement simulate acute appendicitis, meningitis may be suggested by the pain and spasm of the neck muscles; indeed, according to Epstein (1936), there may actually be meningeal involvement, other signs of central nervous system involvement have also been seen. Conjunctivitis, jaundice with or without hepatomegaly, epistaxis, hematuria, rectal bleeding, petechial and purpuric hemorrhages—these and numerous other manifestations are recorded, in fact, Bernstein (1940), in his excellent review, says that on a modest scale infectious mononucleosis may be said to resemble syphilis in its ability to simulate other diseases. Evanescent false positive serological reactions for syphilis have been reported by several observers, Moore *et al.* (1940) say this occurs in about 20 per cent of cases. The patients are chiefly children and young adults, no racial or sex preference has been noted, distribution is world wide. Cases are diagnosed the year 'round but most of the epidemics have occurred in the spring and fall. The period of incubation has not yet been accurately determined, the reported extremes being one and twenty-eight days, relapses are not uncommon and the glandular and hematological changes may persist for years. The causative organism has not been determined (though the isolation of *Listeria monocytogenes* from the throat and blood by Pons and Julianelle [1939] confirming Nyfeldt [1929], is interesting) but the diagnostic value of Paul and Bunnell's laboratory test (the finding of an elevated titer of heterophile antibodies in an individual who has not recently received an injection of horse serum) is being increasingly shown as time goes on. Biopsied lymph nodes do not seem to present a uniform pathological picture, but most authors consider the presence in the blood smear of a certain abnormal lymphocyte, called the 'mononucleosis cell' as almost a pathognomonic sign.

This disease was first described by Filatow in 1880, first definitely envisaged as an acute infectious mononucleosis by Sprunt and Evans, in 1920.

THERAPY

There are no drugs or biologicals which have any specific value. The treatment is symptomatic, recovery without sequelae occurring in practically all cases. There is one report of rapid subsidence of symptoms following x-ray therapy of the tonsils in a protracted case, Lassen and Thomsen (1940) also used convalescent serum with satisfaction, but their series of cases was very small. Bernstein routinely treats the mouth as in Vincent's angina (see Index) because of the frequent complicating presence of the Vincent organisms. Convalescent serum has not yet had sufficient trial to indicate its value. Nolan's (1935) list of 'don'ts' based on experience in an epidemic of 220 cases is probably still good advice: (a) No heat or hot applications to glands. (b) No hot baths in the acute stages. (c) No rubbing, massaging or applications in or about the cervical or inguinal glands. (d) No catharsis. (e) When convalescent, no violent exercise involving strenuous stress about the groin or neck. In Bernstein's experience there has been a remarkable lack of cross infection in patients in close contact with sporadic cases but he feels that strict isolation should be effected upon the appearance of multiple infections.

GRIPPE

(See *Common Cold, Grippe, and Influenza*)

HAVERHILL FEVER

In Haverhill, Mass., in 1926, there was a small localized epidemic of cases which very closely resembled classical rat bite fever (see Index) save for the fact that none of the patients had been bitten by any animal prior to the onset of the illness. A few cases had previously been reported abroad and since the Haverhill report a few scattered cases have been reported both from this and other countries. It now appears that this entity is caused by an organism which has been called *Haverhillia multiformis* and is altogether unlike the spirillum which causes sodoku (rat bite fever). Strangeways (1933) showed that both laboratory and wild rats can act as carriers of this "new" organism—Allbritten *et al.* (1940) have recently reported a case contracted through the bite of an albino rat in the laboratory. However, it is thought that in the Haverhill outbreak the organism probably entered the blood stream through the gastro intestinal tract. Nothing of a definitely differential nature has as yet been noted in the recurrent febrile paroxysms which characterize both the new Haverhill fever and the old rat bite fever, but Allbritten *et al.* feel tentatively that certain other distinctions can be noted.

(a) The bouts in Haverhill are characterized by arthritic symptoms and morbilliform and petechial rashes, while in sodoku joint involvement is extremely rare and there is a papular or large macular rash.

(b) In Haverhill, due to the bite of a rat there is short incubation and no exacerbation of the wound whereas exacerbation of the wound is one of the typical diagnostic findings in classical rat bite fever.

THERAPY

There is as yet nothing distinctive to describe

HYDROPHOBIA

(See *Rabies*)

INFLUENZA

(See *Common Cold Grippe, and Influenza*)

KALA-AZAR

(Visceral Leishmaniasis, Dum Dum Fever)

This disease, which is a very ancient one is common in certain parts of India, in China, Indo China, Arabia, all around the shores of the Mediterranean (where it occurs almost exclusively in young children in the spring and summer), and in southern Russia and central Africa. Until very recently it has been considered not to occur in the western hemisphere except for an occasional imported case, but the studies of Penna (1934) in Brazil disclosed a number of infections there and we now know that even earlier reports had revealed the patchy existence of the disease in several countries of South America. Kala azar is caused by *Leishmania donovani*, a protozoan organism and nearly everywhere that the disease is encountered in man it occurs in dogs also (canine infections occur rarely if at all in India). But little evidence is still lacking finally to incriminate the sandfly as vector. For each locality there must be the right sandfly and the right strain of the parasite. In India the local strain of *L. donovani* and *Phlebotomus argentipes*, in North China the Chinese *L. donovani* and *P. major* var *sinensis*, in Sicily and Malta *L. infantum* and *P. perniciosus*, in Palestine *L. tropica* and *P. papatasi*, and in Bagdad *L. tropica* and *P. sergenti*. Forkner and Zia (1935) finding of viable organisms in the nasal and oral secretions of patients in China has apparently been confirmed by workers in India. It is said that in some instances viable organisms also appear in the urine. The organisms however they may enter the body, embed themselves in the endothelial cells lining blood and lymph vessels particularly in the spleen, liver and bone marrow, whence they burst into the blood or lymph stream to be engulfed by other endothelial cells or by leukocytes. The organism may be cultured *in vitro* and has been established in several experimental animals.

The onset is often insidious though it may be acute. Usually the first complaint is of several bouts of fever with increasing weakness. In one fourth to one third of the cases the fever is of the double remittent type, i.e., with a rise and fall twice or thrice in the twenty four hours. In the majority of cases it is of a very irregular sort. Emaciation and sometimes anemia (proportionate reduction in red cells and hemoglobin) are pronounced and there is a striking leukopenia. Sometimes the body assumes a dusky hue (kala azar—black sickness). Great enlargement of the spleen and later enlargement of the liver, cause the abdomen to be markedly protuberant. In China and Brazil painless adenopathy of the neck has been recorded. Daily rigors are common, though other pronounced symptoms are rare. Manson Baber (1940) says that outstanding features of the disease are the absence of malaria and the maintenance of good appetite. Diarrhea is usually, though not always, due to concomitant bacillary, amebic, or flagellate dysentery. The febrile periods are followed after two to six weeks by afebrile periods and then further attacks of fever. Obtaining the organisms by hepatic or splenic puncture is sometimes necessary in order to make the diagnosis but sternal puncture bids fair to replace these dangerous procedures. Kala azar has decimated whole populations in its time. It is said that Indian villagers have burned alive many of its victims after first stuporizing them with alcohol in the attempt to stamp out the disease. About 90 per cent of the untreated cases succumb in two months to two years.

THERAPY

Pentavalent Antimony Compounds—Antimony sodium tartrate or antimony potassium tartrate better known as tartar emetic, is the classical specific drug in kala azar but its high toxicity the fact that it can only be given intravenously that the time required for the administration of a complete course is very long and that many cases are completely resistant to it from the very start—these things have made it far from an ideal drug with which to attempt the eradication of a disease affecting many hundreds of thousands of people as does kala azar. Therefore the search has been constantly going on for a better drug which seems now to have been found in the form of certain pentavalent antimony compounds that are salts of para aminophenylstibinic acid or substitution products of the same. These compounds are certainly much less toxic than tartar emetic they can be given in larger doses thus reducing the average time required for treatment from two or three months to about three weeks (or to eight or ten days in the case of neostibosan which can be administered daily) and they are suitable for either intramuscular or intravenous injection. Also they are apparently much more effective than the earlier drug there being fewer relapses among those treated with the pentavalent compounds and a considerably lower death rate 4.2 per cent in Napier's series of 107 cases treated with six different pentavalent compounds as compared with 14.4 per cent in his series of 139 tartar-etic treated cases. Unfortunately the new drugs are much more expensive than the tartrates.

Rogers (1939) who originally introduced tartar emetic in India while Christina and Caronia were giving it its first trials in Sicily feels that two of these pentavalent antimonials have shown their superiority to all others neostibosan and solustibosan but I shall also mention several other much used ones.

Neostibosan (von Heyden 693 b)—Napier and Mullock (1929) in India gave a daily intramuscular injection of 0.3 Gm for eight days the total dose therefore being 2.4 Gm. Struthers (1931) in Tsinan feels that the Chinese patient will not tolerate quite such high individual doses. In his series of 87 cases the initial adult dose was 0.1 Gm intravenously and subsequent doses of 0.2 to 0.3 Gm sometimes daily and sometimes every other day the average total dose was 2.63 Gm and the average time under treatment was 23.3 days. In children both intravenous and intramuscular injections were given the initial dose of 0.05 Gm being followed on alternate days by 0.2 Gm average total dose 2.1 Gm and the average time under treatment thirty-two days. Lee and Chu (1935) at the Peiping Union Medical College found an adequate course for a child was 1.5 to 2.5 Gm for an adult, 4 to 5 Gm. Manson Bahr's (1940) total dosage to effect a cure has been 2.7 to 4.0 Gm.

Solustibosan (SDT 561)—This is the first drug introduced as a result of Kikuth and Schmidt's (1938) new method of performing chemotherapeutic studies in infected hamsters. Struthers (1937) in Tsinan used the drug intravenously in neostibosan dosage in 26 cases of this number 22 were discharged cured. Apparently this drug succeeded in some instances when neostibosan had failed and was particularly valuable in late toxic stages in which there was complication by severe cancerous oris. One apparent advantage of this drug is that it is available in the form of a stable solution ready

for injection. It is used intramuscularly and also intravenously and apparently toxicity is lower than that of the other compounds. Yates (1937) has also had fine success with the drug in China, and Napier (1937) in India.

Urea Stibamine—This drug has been much used in Asia. Rogers says that by its use principally the Assam Government cleared up over 300,000 cases between 1923 and 1935. The total amount of the salt given does not usually much exceed 2 Gm, though in exceptional cases it has been run up as high as 10 Gm. Lee and Chu (1935) found an adequate course for a child 1 to 1.5 Gm, for an adult, 1.5 to 2.5 Gm. In Brahmachari's (1931-1933) series of 125 cases, the intensive treatment of adults extended over six to nine days during which the daily dose given intravenously varied between 0.025 and 0.2 Gm, in a later series of 31 cases, daily injections varied from 4 to 16 and the total amount of drug from 0.2 to 2.5 Gm. Manson Bahr (1940) prefers to use this drug in the same dosage, total dose, and time intervals as stibosan (see below).

Stibamine Glucoside (Neostam)—Not used so much as some of the other compounds. Average total dose usually does not much exceed 2 Gm, but in Napier's (1929) series, among 16 patients receiving an average total of more than 4 Gm, there was but one relapse. Struther's (1927) dosage is probably typical, beginning with 0.05 Gm, increasing at each injection by 0.05 Gm until a maximum of 0.2 Gm is reached, however, Napier gives an initial dose of 0.1 Gm, a second dose of 0.2 Gm, and 0.25 Gm for each subsequent dose.

Amino-stiburea—In Napier's series, the average total dose was 2.4 Gm, the average number of injections was 12, and the average number of days under treatment was twenty-nine. The minimum total dose which produced cure for Hodgson, Sen and Das (1928) was 1.5 Gm, the average 2.09 Gm.

Stibosan (con Heyden 471)—In Napier's series (1926) of 104 cases, the average total dosage was 2.78 Gm, the average number of injections (three times weekly) was 13.3, and the maximum dose was 0.3 Gm. Manson Bahr (1940) says the initial dose is 0.1 Gm but may be 0.2 Gm for robust individuals, though it should be reduced to 0.05 Gm for weak patients. He says children tolerate the drug well for a three-year-old beginning dosage is 0.025 Gm, increasing to 0.05, 0.075, 0.1 Gm, and from twelve years up 0.25 may be reached. The drug may be given either intravenously or intramuscularly.

Reactions—The chief reactions when antimony is employed are the following: dizziness, coughing, vomiting, diarrhea, muscle and joint pains, hepatitis (necessitating immediate cessation of the treatment), severe headaches and rigors, pronounced slowing of the heart and frightening cessation of the respirations. When using tartar emetic itself, it is said that a somewhat rare drug-induced complication is acute arthritis which usually beneficently influences the course of the primary disease. With the pentavalent antimonials none of these reactions are upon the whole so severe as those seen during the use of tartar emetic, nor do they occur with anything like as great frequency.

Tartar Emetic.—If the expense of a course of treatment with one of the above drugs were to be very markedly reduced there would likely be no point in retaining a description of methods employed with the classical drug, but since events in the world today seem to be tending to promote

just the opposite effect, I shall still give a brief outline of the use of tartar emetic. As in the last edition of this book it seems to me that the dosage scheme is best presented in a modification of Young's table (Table 5). This drug must be given intravenously since its intramuscular injection is very painful and almost invariably causes necrosis. The solution is sterilized before administration. In infants, in whom intravenous therapy is sometimes impossible, administration of the tartar emetic is often quite difficult. Saha (1931) has reported the successful treatment of 5 cases with rectal injections, introducing 2 cc. of a 0.25 per cent solution after cleansing the rectum with normal saline. The dose is increased 2 cc. in an injection given every second day until 8 cc. have been given then increasing 1 cc. in an injection every

TABLE 5—TARTAR EMETIC DOSAGE IN KALA AZAR

Time	Adults		Children 10 to 15 years		Children under 10 years	
	Cc. of 2 per cent sol.	Gm. of drug *	Cc. of 2 per cent sol.	Gm. of drug *	Cc. of 2 per cent sol.	Gm. of drug *
First week 1st injection	1.5	0.03	1.0	0.02	0.5	0.01
2nd injection	2.0	0.04	1.0	0.02	0.5	0.01
3rd injection	2.5	0.05	1.5	0.03	1.0	0.02
Second week 1st injection	3.0	0.06	1.5	0.03	1.0	0.02
2nd injection	3.0	0.06	2.0	0.04	1.5	0.03
3rd injection	3.0	0.06	2.0	0.04	1.5	0.03
Third week 3 injections of	3.5	0.07	2.5	0.05	2.0	0.04
Fourth week 3 injections of	4.0	0.08	3.0	0.06	2.5	0.05
Fifth week 3 injections of	4.5	0.09	3.0	0.06	2.5	0.05
Sixth week 3 injections of	4.5	0.09	3.5	0.07	2.8	0.055
Seventh week 3 injections of	5.0	0.10	3.5	0.07	2.8	0.055
Eighth week 3 injections of	5.0	0.10	3.8	0.075	3.0	0.06
Ninth week 3 injections of	5.5	0.11	3.8	0.075	3.0	0.06
Tenth week 3 injections of	5.5	0.11	3.8	0.075	3.0	0.06
Eleventh week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.065
Twelfth week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.065
Total		5.27		2.27		1.81

* This column is added by me—H. B.

fourth day to 12 cc. in children up to three years, in a girl of ten years he went up to 24 cc. Rectal irritation was not caused. Most authorities consider that both oral and rectal administration usually fail because antimony is absorbed in insufficient quantities, which may cause the infecting organisms to become antimony resistant or "fast." Intraperitoneal injection in very dilute solution in physiologic saline has been used successfully by Smyly in the cure of a case of kala azar in an infant, aged six months, however, Caroma (1930), whose experience in the disease is vast, has pointed out the at least potential danger of setting up a severe peritoneal inflammation.

Cancrum Oris—In a few cases the slough may be removed and granulation successfully stimulated by the application of silver nitrate, in the beginning as

the stick and later in solutions of decreasing strength Zia and Forkner (1934) have called attention to the occurrence of acute agranulocytosis as a complication of kala-azar and speculate upon the possible connection of this with the appearance of cancrum oris. They did not feel that the agranulocytosis was in all cases caused by the use of pentavalent antimony compounds.

ORIENTAL SORE, DERMAL AND MUCOCUTANEOUS LEISHMANIASIS

Dermal leishmaniasis of the type occurring principally in India after recovery from visceral leishmaniasis responds favorably to tartar emetic and the pentavalent compounds of antimony above discussed, but the mucocutaneous type of the disease, which is prevalent in southern Mexico, Central America, and tropical South America (where it is known also as 'espundia' and 'uta'), is much more resistant. According to Findlay (1939), the trivalent antimonial compound fuadin (see under Schistosomiasis), has been successfully employed in a small number of cases. All of the organic arsenicals have been tried with indifferent success, so also many other drugs: quinine, Bayer-205 etc. That is to say, the gamut of specifics is being run in the hope of finding one that will cure this disease. Some observers (de Rezende 1925) have found curettage and the local application of 80 per cent lactic acid superior to any other treatment. Pupo (1935) reported good results with intramuscular injections of sodium arsenite, 1/60 grain (1 mg.) to the cubic centimeter. The twice weekly injections begin with 2 cc. and increase after the first two weeks until 5 cc. is given at each injection; the total treatment lasts thirty to forty five days. It is interesting to note that Shattuck's (1936-38) investigation yielded circumstantial evidence that American leishmaniasis is transmitted by a winged biting insect which lives among trees or shrubs and that in nearly all regions indigenously affected a species of *Phlebotomus* which bites man is known to occur. It is considered likely that a reservoir of the virus exists in one or several species of wild forest animal, or perhaps even in a reptile or plant.

In oriental sore the antimony preparations are of considerable value but do not regularly exhibit the high degree of specificity seen in kala-azar. Since the disease is not fatal and usually pursues a self-limited course of from six to eighteen months many students of the subject doubt the advisability of combating it with such potentially dangerous drugs. Excision of the lesion has been successfully performed. The most interesting departure in treatment recently reported is that of Akrawi (1940), who applied one of the sulfonamides (sulfapyridine) directly to the sore in powder form after cleansing with saline solution. He says that 63 per cent of his 72 cases were cured in a month's time. Emetine hydrochloride has been injected in solution subcutaneously and intracutaneously around and beneath the lesion. Sinderson (1925) obtained excellent results with a 2 per cent solution and 1 injection only in a series of 147 cases. Berberine sulfate is also successfully injected locally. Karamchan-dani (1927), using $\frac{1}{2}$ gram (0.015 Gm.) dissolved in 1.5 cc. of distilled water, obtained healing in fourteen days in 5 cases as compared with eighteen days in a tartar-emetie treated series—a significant difference when the nature of the two types of treatment is taken into account. Warma (1931) and de Castro (1931) confirmed these results. Devi states that of 18 sores on 12 patients 6 healed completely after 1 injection, 5 after 2 injections and 5 after 3 injections.

tions In Hayward's (1933) experience of over 300 cases, all receiving 5 or more injections were cured, but the treatments were sufficiently painful to drive away many patients

LEPROSY

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis, and yellow fever, and since they do not nowadays raise problems in treatment for the general practitioner I shall no longer allot space to a consideration of them in this book.

LEPTOSPIROSIS

(Weil's Disease, Spirochetal Jaundice)

This is an acute infectious disease caused by *Leptospira icterohaemorrhagiae*. Onset is usually abrupt with vomiting, headache, fever, muscular pains, especially in the calves of the legs and the abdominal wall and great prostration, sometimes there is initial chill or chilliness, transient stiffness of the neck, labial herpes, hiccup and cough, conjunctival injection is often present. There is leukocytosis of high degree and nosebleed or other forms of hemorrhage are of frequent occurrence. The urine early contains bile and may show all the evidences of acute toxic nephritic or nephrotic changes. In about half the cases the temperature falls in three or four days to a week and the patient goes on to recovery, but in the other cases jaundice of unknown causation appears at about the time the temperature falls and the liver becomes tender and swollen, the spleen may be palpable. In these severely ill patients there is an increase in the hemorrhagic tendency and often renal failure occurs, delirium or semi-coma and a morbilliform, purpuric or scarlatiniform rash often appears, but the temperature usually remains low. On the Continent a meningeal form of the disease is recognized and Ashe *et al.* (1941) state that it occurs in our country also. In those surviving the severe attack defervescence usually begins at the end of the second week, but there are sometimes one or more mild relapses and convalescence is often very protracted. Leptospiroid vegetative endocarditis, iridocyclitis (and much more rarely optic neuritis) have been recorded as late complications.

The causative organism is present in the blood up to the seventh day and appears thereafter in the urine where it persists for a long while after recovery. It seems that darkfield examinations for *L. icterohaemorrhagiae* are very misleading. The blood also gives a positive agglutination reaction, Ashe *et al.* say that if this reaction is negative after thirty days Weil's disease may be ruled out, a statement which certainly does not indicate that much diagnostic aid

is to be expected from this test early in the attack. The newest laboratory contribution consists in injecting blood from the patient into a young guinea pig, the animal becomes febrile in a few days and it is said the organism may then be demonstrated in its aspirated peritoneal fluid. The same organism is found in wild rats the world over and it is significant that most recorded sporadic or epidemic cases have occurred in individuals who have passed some time in wet, rat infested places, such as military trenches and civilian excavations, natural swimming pools, mines, sewers, dirty canals, rice paddies, dank fish handling establishments and slaughterhouses, or have drunk water from such places. One American outbreak was presumably traced to infected holy water in use during a religious novitiate. Insects have been shown not to be intermediary hosts, the water or slime being infected directly from the urine of the rat, *L. icterohaemorrhagiae* will live in stagnant water for three weeks. The organism has often been found in the urine of dogs, cats, foxes, field mice, pigs, and horses, laboratory workers have become infected from albino rats that had been infected by wild rodents, guinea pigs are occasionally, but white mice more often, carriers of the disease. The organism has been passed from dogs to man in a number of instances but passage from dog to dog has not been proved, which indicates that the dog likely obtains it from the carcass of one of the other carrier animals, but there is a serious infectious jaundice in dogs (dog typhus or Stuttgart disease), which is caused by *L. canicola*, man has been infected by contact with these dogs, but this canine organism does not occur in rats. Man to-man infection with *L. icterohaemorrhagiae* is apparently very rare though a case has been reported of transmission by copulation and it seems that intrauterine infection of the fetus can occur.

Weil's disease occurs all over the world and in some areas the incidence is rather high, undoubtedly we will find many more cases than hitherto reported in the United States when we begin to look for them. Males preponderate among the patients and children are rarely affected, most cases occur during the summer. In an epidemic among laborers in the Andamans, the onset of the first case was six days after the beginning of work in a leptospira infected swamp, Schuffner (1934) found an average incubation period of 10.3 days in 452 cases in Holland. Mortality, usually between 5 and 10 per cent, may reach as high as 60 per cent in some epidemics, to date it has been about 30 per cent in the United States.

Weil first described this disease in 1886, and Inada and Ido discovered the causative organism in 1914.

THERAPY

One would be hopeful of the intravenous arsenicals here, but they have failed, indeed, some cases have been made worse by their use, probably because of the state of the liver. The antimonial drugs have also failed. Studies with experimental animals have indicated that bismuth might have real value, but years have passed and there has still been no thorough trial in the human. The earlier sulfonamides were tried unsuccessfully. An apparently potent antiserum prepared by raising the agglutinating titer of horse serum was originated in Japan and is successfully and widely used there and in Europe, but it is still not available in the United States. In Hawaii the serum has been obtained from Japan and used satisfactorily by Tokuyama (1940).

Davidson and Smith (1939), in Scotland, say that 10 to 20 cc is given intra muscularly or intraveaously and the dose repeated in four to six hours, but Tokuyama says he strictly follows Inada and Ido's instructions to give 40 cc intraveaously every twenty four hours. Also in Hawaii, Keay (1938) successfully employed transfusions from a convalescent donor and obtained "spectacular" results in his two cases. Asbe *et al* (1941) also transfused convalescent blood in a single case—the patient had been anuric for thirty hours but began to void six hours after the transfusion, antihodies previously absent, appeared in, and leptospira disappeared from, the blood. In Japan large scale employment of horse antiserum has been made in prophylaxis, but Walch Sorgdrager (1939) says that this is not routinely done in Holland even in the case of an individual who has fallen into one of the highly infected canals only 1 in 75 such persons contracts the disease and to such a one the serum is administered upon the first appearance of symptoms. However, in that country recently, Schöffner (1941) used prophylactic injections in 21 individuals who had been exposed through handling a colony of infected rats but he employed a vaccine made from rich cultures of the organism subjected twice for thirty minutes to 70° C, and injected intravenously, first 1 cc and on the eighth day 2.5 to 3 cc (a few reactions of an allergic nature he felt could have been avoided if the second injections had been given on the sixth day).

The dejecta, being infectious, had better be disinfected and disposed of and the attendant's hands as well cared for as in typhoid fever. Cotter and Sawers (1934) concluded that carriers are probably not important in spreading the disease, there would likely be no point in keeping the patient in hospital until the urine is free from organisms.

MALARIA

This day relenting God
Hath placed within my hand
A wondrous thing and God
Be praised At His Command

Seeking His secret deeds
With tears and toiling breath
I find thy cunning seeds,
O million murdering Death

I know this little thing
A myriad men will save
O Death where is thy sting
Thy victory O Grave!

Before Thy feet I fall,
Lord who made high my fate
For in the mighty small
Is shown the mighty great

—Lines written by Ronald Ross on finding himself in possession after infinite toil of conclusive proof of the causal relation of the mosquito to malaria

Malaria is an infectious disease caused by plasmodia conveyed from infected to healthy persons by the bite of the females of certain mosquitoes of the subfamily *Anophelinae* in whose body the organism passes a part of its life cycle. It is the most important disease, infectious or noninfectious, with which mankind has to contend, for it kills more people than any other and

tremendously curtails the socio-economic efficiency of those who survive. This is true even today though the incidence of the malady has greatly declined in the more northern civilized countries, in the subtropics and tropics throughout the world it still reigns supreme. According to a recent estimate 800 000,000 people suffer from this disease, and Sinton (1936) says it causes well over a million deaths each year in India alone, being responsible 'directly and indirectly' for a total of two million deaths there. The estimated annual financial loss to the British colonial empire occasioned by malaria is \$200 - 000,000. In our own tropical possessions we are somewhat better situated for the disease is not present in Hawaii and though there are 10,000 to 20,000 deaths annually in about 2 000 000 cases in the Philippines the situation there is not at all comparable with that in British and Dutch Malaya. In our West Indian possessions and in many of the newly acquired military and naval bases, malaria constitutes a serious menace. (Interestingly in passing, it is worthy of note that Robertson [1940] of the League of Nations Epidemic Commission believed that malaria was likely to do more damage than the Japanese air force along the famous Burma road, Williams [1941] of the United States Public Health Service, studying the situation for the Chinese government certainly supported this opinion.) Surgeon General Parran (1940) has said that of the many military medical and health problems in the tropical Americas, the most important is malaria. In the continental United States the disease has held sway in its time from the Gulf of Mexico to the Great Lakes (including extension well up into Canada) and from the Atlantic seaboard to well past the Mississippi River, indeed, with the beginning of extensive agriculture on the West Coast and the incursion a few years later of successive migratory waves and the horde seeking gold in 1849, malaria became established first epidemically and then endemically along our Pacific seaboard. But the recession from the north began according to Boyd (1941), as early as the 1890's, the disease has now nearly disappeared from practically all the states north of the Ohio River, except for limited regions of benign tertian endemicity and there seems to have occurred also a decrease in intensity even in the endemic areas where it persists. Still, one can never be sure of trends in this disease, as was so devastatingly shown in the great epidemics in Ceylon and Brazil a few years ago, in fact in recent years malaria has reappeared in many areas in our South from which it had apparently disappeared a little while before and it is also spreading into adjacent territories in which the populations are presumably less immune. It has been said that the annual cost of malaria to the South—Faust (1939) estimates that there are 1 500,000 cases—is \$100 000,000.

Malaria was well known to the ancients. Garrison, quoting Sir Harry Blake, says that the theory of its conveyance by mosquitoes was indicated even in the Sanskrit *Susruta*, while another author holds it responsible for the vacillation of the Greeks before Troy. Williams (1941) says that a Chinese manuscript of the third century B.C. advises the traveller entering regions where *chang-chi* ('malicious air') prevailed to make arrangements for the remarriage of his widow. Hippocrates gave classical descriptions of malaria. It has been learnedly held that this ailment, by driving the population cityward, was a pronounced causal force in the final decline of the Greek civilization, and that the later Roman Empire must sooner have succumbed to attacks from the north had not the barbarian hordes been decimated by the

ague The Middle Ages knew its ravages, too, while in many a military campaign of the eighteenth and nineteenth centuries more men fell victim to chills and fever than succumbed to shot and shell The French failure to construct the Panama Canal was due in large part to this disease, and in World War I malaria was one of the chief causes of disability at troop concentration areas within the "malaria zone", after the War the return of troops and the interchange of people caused its reappearance in many places long free of it England, Germany, Russia (one of the worst epidemics in history), far up in the arctic at Archangel The direct toll of malaria in World War II is currently being exacted

Laveran discovered the causative organism in 1880 but the modern sanitarian's attack upon the disease did not begin until after Ross, Grassi and others in 1898 had incriminated *Anopheles* mosquitoes as the vector

When the mosquito bites a malaria infected individual she takes into her stomach two forms of the plasmodium schizonts and gametocytes, the latter being called "crescents" in the case of malignant subtertian infections The schizonts are destroyed just as any other food substance, but the gametocytes, which are sexual forms, survive, fertilize, and eventually give rise to active sporozoites which make their way into the salivary glands and are then injected into the blood of an individual subsequently bitten by the mosquito Precisely what becomes of these sporozoites in the human body we do not know, but the possibility that they tide over the incubation period in the recently-discovered exo-erythrocytic form is fascinating at any rate after a time, having undergone a metamorphosis somewhere, they reappear as plasmodia in the red blood cells, where they mature and finally erupt into the blood stream as a shower of schizonts (asexual forms) and gametocytes (sexual forms) The gametocytes cause no symptoms and finally die if not taken out of the blood again by a mosquito, but the schizonts reenter fresh red blood corpuscles and repeat the cycle, giving rise to the symptoms of the disease In the typical, moderately severe case of benign tertian malaria (*Plasmodium vivax*), the patient presents a swollen and sometimes painful spleen (and often liver), herpes simplex about the mouth, and the organisms in the blood, he is a weary, worn, anemic and perhaps jaundiced individual, appetiteless spiritless with oftentimes headache and backache and a host of other ailments in addition to his paroxysms of chill (often accompanied by vomiting), fever and sweating which occur once in every forty-eight hours (usually between midnight and early afternoon) and last six to ten hours If there are present two generations of parasites, maturing on successive days, there will then be what is called double tertian infection and consequently daily (quotidian) rigors, not infrequently an initial remittent, typhoid like temperature may also confuse in these cases The infrequently seen quartan type of the disease (*P. malariae*) is characterized by paroxysms every seventy two hours, but there may be double or triple quartan infections which break up the regular periodicity of the attacks—and in quartan also the fever in the primary attacks may be remittent instead of intermittent Malignant subtertian or estivo autumnal malaria (*P. falciparum*) is the most dreaded of the several forms of the disease, for, though not regularly paroxysmal and sometimes causing merely malaise and low fever for a considerable period, it is capable of very suddenly involving the patient in attacks of the most diverse nature, to which have been given collectively the title "pernicious malaria" The

is already recognized that numerous more or less permanent residuals of a neuropsychiatric nature are chargeable against the disease doubtless due to embolic or hemorrhagic damage during the cerebral type of paroxysm, and I imagine that in the course of years a somewhat sharper picture than is now visible of chronic malaria will be drawn i.e., we will recognize more than mere "cachexia" as characterizing this state. Meanwhile, and particularly in view of the amazing alterations in transportation facilities in recent times and the current activities of our great army and navy establishments the general practitioner (no matter how far north he may reside) is well advised to remember that even acute malaria is by no means always easy to diagnose and that in either the acute or chronic form the manifestations of infection with the malaria organisms may simulate almost any other syndrome. Malaria is extremely likely to provoke false positive Wassermann and Kahn tests (Moore *et al.*, 1940 say this occurs in 100 per cent of cases at some time during the infection), but no satisfactory serological tests have been devised for malaria itself. Failing to find the organisms in the blood, the finding of leukocytes containing pigment is considered proof of infection confirmatory evidence is leukopenia with relative increase in large mononuclear cells (but there may even be leukocytosis), and a deep sherry color (urobilin) in the urine in latent malignant subtertian cases. During the course of an attack the blood sedimentation rate cannot be definitely correlated with the clinical findings.

It is generally said that the average incubation period of malaria is ten days but perhaps fourteen would be more accurate extremes of one to forty weeks are on record. In the north temperate zone some of the benign tertians seen in the spring and early summer are relapses but many of them are primary attacks resulting from the organism's ability to hibernate in the body during the winter (the infecting bite having occurred in the preceding autumn), in midsummer and autumn both primary attacks and relapses occur. In this zone most malignant subtertian cases are seen in late summer and early fall, in the south temperate zone these matters are reversed with the seasons of course. In the tropical zone infections with the benign as well as the malignant tertian parasite ordinarily give rise to attacks at once after the usual incubation period, but even in these torrid lands there is a seasonal periodicity of malaria not always easy to account for, the interested reader is referred to Col. Gill's (1938) exhaustive and fascinating book on the subject.

Latterly, instances are accumulating in which malaria has been induced through the transfusion of blood and it would seem that under present-day methods there is no certain protection against this, for Hutton and Shute (1939), of the well known Horton Hospital group in England, assure us that all the species of plasmodia can survive for weeks at the temperature of 4° C (39.2° F) at which blood is stored though it must be admitted that Antschelewitsch (1937) failed to transmit the disease in every one of 11 transfusions in which the known malarious blood had been stored more than eight days. Routine search of blood smears for organisms will not clear the donor because at most hospitals there is no one sufficiently experienced to detect the very occasional parasite in a thick film. The best safeguard would seem to be to use as donors only individuals who could not conceivably ever have become infected—a precaution which it is going to become increasingly difficult to practice in this country of ours. In the event that it is foreseen that a suspected

application, second, it required an amount of persistence in treatment seldom attainable, third, its success in preventing relapses was very little if at all better than with the method of the patient who took his drug only long enough to control the symptoms in each attack. The Malaria Commission of the Health Organization of the League of Nations (in its now famous Third [1933] General Report) sought to utilize the newer immunologic knowledge in a practical way by advocating that treatment should await determination of the species of the infecting parasite, the virulence of the particular strain, and the resistance of the patient. This doctrine was at once vigorously opposed by experienced tropical practitioners, and it is certainly the consensus today that to delay treatment until the temperature comes down or to permit the occurrence of several paroxysms with the object of inducing immunity, is to expose the patient to very grave risks. But the Report, in its pronouncement in favor of a shorter course of treatment, did serve excellently to crystallize the conviction that this is the preferable type of therapy. The short course treatment, consisting of the use of specific agents for only a few days during the initial attack and then during each of the relapses, has the great and practical advantages of (a) relative inexpensiveness, (b) ease of accomplishment. Therefore, in view of what has been said above, together with the facts that the Malaria Commission (comprising leading malariologists of many countries and basing its findings upon observations of results and effects in 12,288 individuals) in its Fourth General Report (1938) reasserted its advocacy of the short term treatment, and that the same is being employed with success throughout the world (but not without the knowledge that a few men of experience, notably Craig [1940] are holding out against it) I shall take the position here that "short term" therapy is the method of choice in treating malaria.

ACTIONS OF THE SPECIFIC DRUGS

Of all the agents which have been proposed for the treatment of malaria only four have really earned a place as true specifics: good old quinine, brought to Europe as cinchona bark in 1632 and isolated in alkaloidal form in 1820, plasmochin, a synthetic substance unrelated chemically to quinine introduced in 1932, atabrine, another unrelated synthetic made available in 1936, and the newest synthetic just introduced a little while ago—certana. The place of these drugs in the therapy of malaria is definitely fixed and delimited as follows: (a) quinine and atabrine control the acute attack by destroying asexual forms of the organism in all types of the disease and to some extent they lessen the patient's infectiousness for mosquitoes by partial destruction of the sexual forms, though this latter action is less pronounced in malignant tertian than in the other types, (b) plasmochin is not very effective against acute symptoms but when used alone after the use of quinine or atabrine has ceased it is quite effective in lessening the incidence of relapses, it is also the most effective agent in ridding the patient of the sexual forms which infect the mosquito, (c) certana, which has not yet been fully studied, is used in place of plasmochin as it is alleged to be less toxic.

CHOICE BETWEEN QUININE AND ATABRINE

I can assure the reader that this has become an extremely controversial matter. In the sections below I am setting up a typical method of attack with either of the drugs, in both benign and malignant cases the following being

a few citations from the prodigious literature of the subject indicating why it is presently impossible to recommend one of the drugs while dogmatically excluding the other. In the Fourth General Report (see above) the Commission stated that in the individual treatment of an ordinary case of benign tertian it seems immaterial, save for financial considerations (atabrine being in most places the more expensive), whether quinine or atabrine be used. Clark *et al* (1941), of the Canal Zone, agree with this though making the additional point that atabrine is easier to take. Either drug, if begun during or just at the conclusion of the first paroxysm will often diminish the severity of the second and prevent completely the occurrence of the third. Smith (1939), in India, thinks the two drugs about equally effective in comparable dosage but, recognizing that quinine is a bit quicker in action, he prefers to give it for the first two days and then begin with the atabrine, this was essentially the conclusion of Amy and Boyd (1936) from a study of the entire malaria statistics of the British troops in India. quinine until the febrile paroxysms are controlled, then a course of atabrine. Lapscomb (1939), in the same country, sees no significant difference between the two drugs though he prefers atabrine. Most studies are not confined to benign or quartan cases alone and the inclusion of malignant subtertians confuses the picture because of their greater initial severity and higher relapse rate. Considering the treatment of all types of cases in the Canal Zone over a number of years, Gentzkow and Callender (1938) state in no uncertain terms that atabrine is inferior to quinine in preventing relapses, but admittedly the report includes many types of employment of both drugs. In Russia, in an apparently carefully controlled study in 1485 patients Fas-touskaja and Cenderowitch (1938) found atabrine slightly superior for the same purpose, Siegenbeek van Heukelom and Overbeek (1938), in the Netherlands Indies agree. But Hall (1941), in Nigeria, says the relapse rate appears to be high with atabrine and he remarks that it 'does not suit all patients'. Barrowman (1940), in British Malaya, says there are certain strains of the parasite which do not respond to atabrine. On the same he id, Manson Bahr (1941), discussing the types of severe malignant subtertian infections which the British were encountering while invading Libya, said that atabrine could not compete with quinine in bringing these cases under control, he had earlier said that if atabrine is being used in stubborn malignant subtertian cases 5 to 10 grains (0.3 to 0.6 Gm.) of quinine should be used at the same time. Hasselmann's (1919) experience in the Philippines is that racial and climatic differences have always to be taken into account in treating malaria and that in the tropics the treatment of all cases of malignant subtertian type should begin with large doses of quinine—he considers, in fact, that this has not only been the teaching of Castellani, James, Watson, and others but that experience in the terrible Ceylon epidemic in 1935 emphasized its importance.

Atabrine is now manufactured in Germany, France (or was before the Germans overran the country), Italy, Russia, England and the United States, so there is no danger of "running out" of this drug. The Netherlands Indies are the source of 97 per cent of the world's supply of cinchona and the quinine obtained from it. At the close of 1941, Taylor stated authoritatively that there were ample supplies of quinine in this country, the United States Government having purchased nearly ten million ounces and many manufacturers having in addition stocks enough for at least two years' needs. Small amounts of cinchona are produced in India and it was said in 1937 that enough total

alkaloids were being produced in the Philippines to supply those islands if the necessary extraction facilities were made available. I have heard that large experimental cinebona plantations have been started in Central America.

TREATMENT OF BENIGN TERTIAN OR QUARTAN CASES

Quinine and Atabrine Dosage.—In the earlier of its two principal Reports, above referred to, the League of Nations Malaria Commission favored an average adult dose of 10 grains (0.65 Gm.) of quinine daily for five to seven days; in the later Report, however, 15 to 20 grains (1.0 to 1.3 Gm.) is favored and it certainly seems that experience in many quarters is indicating the wisdom of this larger dosage. Some men now give 15 grains daily for a week, some give 20 grains for the same time, some give 30 grains until the failure of a paroxysm to appear (almost certainly the third will not appear if treatment was begun during the first) and then 15 grains for an additional week, and a few insist upon 30 grains for one full week from the beginning of therapy. The dosage for children, as employed by Hill and Olavarria (1935) in their studies in Puerto Rico for the International Health Division of the Rockefeller Foundation, are: under one year, $1\frac{1}{2}$ grains (0.1 Gm.); first and second years, 3 grains (0.2 Gm.); third and fourth years, 5 to 6 grains (0.3 to 0.4 Gm.); fifth to eighth years, 8 to 10 grains (0.5 to 0.6 Gm.); ninth year and up, 12 to 15 grains (0.75 to 1.0 Gm.). The above scheme certainly does not err on the side of under dosage but children bear quinine well.

For adults the atabrine dosage is $4\frac{1}{2}$ grains (0.3 Gm.) daily for five to seven days, most men now favoring the full week's course. For children, who tolerate this drug well also, Manson-Bahr (1940) recommends the following daily dosage: up to one year, $\frac{1}{4}$ grain (0.05 Gm.); from one through four years, $1\frac{1}{2}$ grains (0.1 Gm.); from five through eight years, 3 grains (0.2 Gm.); from eight upwards, the adult dose of $4\frac{1}{2}$ grains (0.3 Gm.).

Timing of Doses.—It is the almost universal custom to give the first dose of either drug as soon as the diagnosis is made and thereafter to give one-third the daily total dosage after each of the three meals (atabrine particularly is better borne upon a full stomach). Manson-Bahr (1940), however, says there appears to be an advantage in giving quinine more frequently, i.e., breaking up the daily dosage into 6 instead of 4 portions. In the old days it used to be customary to give most of the drug (quinine only was used then) just before the paroxysm was expected, quite the reverse of Manson-Bahr's idea of spreading it out through the day as much as possible. Recently, Dauncey (1941) has sought to revive this method by citing that during a long experience in India he always got best results when giving quinine an hour to an hour and a half before the expected rise in temperature.

Preliminary Catharsis.—It is the custom of many physicians to precede or accompany the first dose of quinine or atabrine by a dose of calomel, followed as usual with salts after eight or ten hours. This seems to me an old-fashioned custom which might as well be given up, but perhaps I do not know enough about the subject to pass this judgment—certainly anyone familiar with our own South knows that a prodigious amount of calomel is taken by the populace in malarious regions there. Someone should investigate this matter—why, for example, will an individual absent himself from

some meeting of friends because he must take his "course" (same being calomel and salts) though nothing could force him to submit to a periodic dosing with quinine. Perhaps something underlies this faith in calomel.

Quinine Preparations—The least expensive and most used salt is the sulfate given in capsules or tablets. The hydrochloride or the dihydrochloride or the alkaloid itself may be used in the same dosage as quinine sulfate but any of them is more expensive and no better than the sulfate. All of these drugs are relatively insoluble but if the capsule opens or the tablet is held more than a moment there will arise nevertheless an intensely bitter taste in the mouth. There is strong temptation to prescribe ready made chocolate or otherwise coated pills but these are often stony hard and may pass through the intestinal tract undissolved. Quinine ethyl carbonate (euquinine) is so insoluble as to cause little taste and is much given to children in the same dosage as the sulfate, it is considerably more expensive. There has always been disagreement regarding the proper dosage of quinine tannate, another insoluble salt, and it has been omitted from the USP XI. Quinine bisulfate is sufficiently soluble that it may be prescribed in solution but it has a lower alkaloidal content than the other salts and should be given in one third larger doses—about 13 grains (0.8 Gm) of the bisulfate instead of 10 grains (0.65 Gm) of the sulfate. The following prescription is about the best that one can do in the way of disguising taste (and little enough it is!)

\mathcal{R} Quinine bisulfate	$\overline{\text{Siiss}}$	14 0
Aromatic syrup yerba santa (eriodictyon) to make	$\overline{\text{Siv}}$	120 0
Label: As directed (4 teaspoonful contains the equivalent of about 5 grains [0.3 Gm] of quinine sulfate)		

In American military circles the pleasant little custom seems to prevail of bringing the sulfate into simple unflavored solution in water by the addition of concentrated hydrochloric acid at the rate of 1 drop of the acid and 5 grains of the salt to a drachm of water. This barbarism is best not attempted in civilian practice. Of course there are hoards of expensive quinine solutions and suspensions on the patent medicine shelves and they are much resorted to by patients who as pointed out by Fernan Nunez, do not believe in quinine but will take anything called a "liver tonic." As an ethical preparation the Council on Pharmacy and Chemistry has accepted the *Coco Quinine of Eli Lilly and Company*, a chocolate vanilla and yerba santa flavored suspension containing 10 grains (0.65 Gm) of quinine sulfate per ounce. This *Coco Quinine* is somewhat expensive of course but it is a splendid preparation to use in children if there is difficulty in getting them to take the drug disguised as in the above prescription, or one may try the method suggested by Reed (1940) dissolve 5 grains (0.3 Gm) of quinine dihydrochloride in 4 teaspoonfuls (15 to 20 cc) of water and add a little honey, syrup or jelly—one fourth of the solution will contain about $1\frac{1}{4}$ grains (0.08 Gm) of the drug.

Atabrine Preparations—Atabrine is commercially available for oral use in the form of $\frac{1}{4}$ gram and $1\frac{1}{2}$ gram (0.05 and 0.1 Gm) uncoated and $1\frac{1}{2}$ gram (0.1 Gm) sugar-coated, tablets, I think the former should be preferred because they may be swallowed quickly before the bitter taste develops and there is no chance of them passing through the intestinal tract undissolved. For children the tablet may be crushed and suspended in honey or syrup.

Manson-Bahr (1940) says it is best given to them in milk or hidden in a raisin

Plasmochin and Certuna to Reduce Relapse Rate—It seems to have been amply established by many men of experience (Lipscomb, Smith, Gentzkow and Callender, Amy and Boyd, Manson Bahr, among those already cited above) that if plasmochin is used during the acute attack the incidence of relapses will be reduced. But it must not be used at the time atabrine is being given as each drug intensifies the toxicity of the other. Most men also wait until the quinine course is completed before giving it, the usual method being to wait two days after the end of a quinine or atabrine course and then begin the plasmochin and give it for five days in adult dosage of $\frac{1}{2}$ gram (0.01 Gm) three times daily. Manson Bahr gives the daily dosage of plasmochin for infants as $\frac{1}{120}$ gram (0.005 Gm), one to five years, $\frac{1}{4}$ gram (0.01 Gm), five to ten years, $\frac{1}{2}$ to $\frac{3}{4}$ gram (0.01 to 0.02 Gm). However, some men still give plasmochin while the quinine is being given, either in the form of quinoplasmin (heprochin) tablets containing 5 grains (0.3 Gm) of quinine sulfate and $\frac{1}{4}$ gram (0.01 Gm) plasmochin, or as plasmochin compound tablets containing only 2 grains (0.12 Gm) of quinine plus the $\frac{1}{4}$ gram (0.01 Gm) of plasmochin. One attempting to give full quinine dosage in the form of either of these mixtures, particularly the plasmochin-compound, is likely to be giving excessive amounts of plasmochin for all authorities agree that the total daily dosage of this drug should not exceed $\frac{1}{2}$ to 1 gram (0.05 to 0.06 Gm).

It is claimed for the new drug, certuna (cibonal), that it is as effective as plasmochin and causes no disagreeable symptoms at all, but there have been few observations in the field as yet. Lipscomb's dosage was $\frac{1}{4}$ gram (0.02 Gm) three times daily.

Quinine During Menstruation, Pregnancy, and Lactation—It is alleged that quinine taken during menstruation will diminish the flow or increase it if there is a tendency toward menorrhagia, however these things are not established and not taken into account when the drug is imperatively needed. Traces have been detected in the milk but they are insignificant as regards effect upon the suckling infant. Balasquide (1939) states that there is a general belief in Puerto Rico that quinine dries the maternal secretions but he knows this to be unfounded. Regarding pregnancy, it is established that extensive infection of the placenta with the malignant subtertian parasite is very likely to cause the death and premature expulsion of the fetus. Blacklock and Gordon many years ago found that more than a third of the placentae of West African native women examined by them contained large numbers of organisms, and that 25 per cent of the children of these women died within a week. It is agreed by all observers also that malaria of any type may be dormant until awakened during labor, at which time the first typical pyrexial attack may occur. So much for the undoubted effect of the disease upon the pregnant woman, but of the effect of quinine upon her there is a difference of opinion. In some parts of the Far East the feeling is widespread, and apparently fostered by European practitioners, that periodical dosage with quinine predisposes to abortion. Thus Manson Bahr states that he has treated pregnant patients at term who were suffering from advanced malarial cachexia but had been strictly forbidden by their medical attendants to take quinine in any form, his own feeling is that

pregnancy does not contraindicate the use of the drug altogether but that the minimum dosage likely to be effective—say 3 grains (0.2 Gm.) repeated every eight hours for two days—should be employed. Wickramasuriya (1937) who has given much attention to this matter in Ceylon is convinced that full quinine dosage should be given and that the concomitant use of bromides holds the oxytocic action of quinine fully in abeyance. Indeed he has known this treatment in many instances to prevent abortion which seemed imminent under the influence of malaria. Balasquide in Puerto Rico also feels that the drug is not contraindicated. Interestingly Smith in the United States a few years ago reported satisfactorily upon the employment of $1\frac{1}{2}$ grains (0.1 Gm.) three times daily for three weeks prior to expected confinement in 60 presumably nonmalarious women for which he considered its general tonic effect.

One other thing needs to be mentioned however—it seems that quinine given to the pregnant woman is capable of causing serious visual and aural disturbances in the infant; this has occurred extremely rarely to be sure but it has occurred (see Taylor, West, Richardson and Forbes in the Bibliography).

It is heralded as one of the great advantages of atabrine that it may be more safely used than quinine in pregnancy and this is very probably true but Wickramasuriya says it would appear that the drug is contraindicated in the toxemias of pregnancy.

Toxicity of the Specific Drugs.—On the now outmoded long-course standard method of treatment with quinine it is not unusual for patients to be made very uncomfortable by one or more of the following symptoms: nervousness, headache, giddiness, palpitation, tremors, nausea, disturbances of sight and hearing. Sodium bromide 2 grains (0.12 Gm.) for every 1 grain (0.06 Gm.) of quinine is often given to control these symptoms. Fernan Nunez (1941) says that the use of a small amount of ergot is also often helpful. Occasionally loss of sight and hearing have occurred and return of complete function has not always taken place upon cessation of the administration of the drug; however such serious poisoning occurs very rarely (see however the discussion of the use of quinine in pregnancy for further reference to this matter). It seems that most individuals are disturbed somewhat even by the usually smaller doses employed in the modern short-course method but one would expect serious disturbances to be at a minimum when the drug is given for only one week; indeed many individuals can take 15 grains of quinine daily for a much longer period than that with little more disturbance than ringing in the ears. Idiosyncrasy is quite another matter; however for patients truly hypersensitive to the drug may be upset by very small doses. The most usual signs of idiosyncrasy are skin rashes, gastro-intestinal disturbances, coryza, pseudo-asthmatic and anginal phenomena, hemorrhagic disturbances (including the blackwater fever type of syndrome) and agranulocytosis have been reported and since this is an allergic type of reaction almost anything can be expected.

The substitution of quinidine for quinine in cases of idiosyncrasy to the latter drug has been shown—principally by Sanders (1930-1936) and his associates—to be feasible. In their experience there have been only a few instances of separate idiosyncrasy to quinidine.

Atabrine, not being obtained from cinchona bark, can be substituted of course with complete success in any case of idiosyncrasy to a cinchona alkali.

loid Due to this fact desensitization to quinine is not attempted nowadays and I shall therefore not include a description of the methods in this edition of the book.

Atabrine—Atabrine is yellow and causes the urine to assume the same color on about the third to fifth day (the first indications of this may be had by adding a few drops of acetic acid, heating and looking down the test tube against a black background), in some instances yellow discoloration of the skin (but not of the sclerae) also occurs. This discoloration is entirely due to the acridine dye nature of the drug and not to jaundice indicative of liver injury, it usually disappears in one to two weeks though persistence for several months is on record and patients are routinely well advised to keep out of direct sunlight for a month following an atabrine course to lessen the likelihood of this occurring. Other annoying but neither serious nor very frequent symptoms are headache, abdominal pain, nausea and diarrhea any of which are likely to last for several days after the drug is discontinued. Atabrine does not cause visual or aural disturbances and is usually preferred to quinine by the patient who has had experience with large doses of the latter. I have heard individuals say that they were actually stimulated by the drug and others have reported the same thing, but I am frankly sceptical of the occurrence of this effect, since word of the type of reaction to be mentioned momentarily may have spread widely through the malaria country.

In a low proportion of cases (but with reports from all over the world so that there can be no question of a racial predisposition) actual psychoses have been caused by the drug they have been usually mild and transient affairs but some patients have presented wild manic states gradually merging into somnolent delirium and even deep coma lasting several days to a week. Permanent derangement has not been reported. Kingsbury (1934) believed that mental predisposition was an important factor in these cases, Turner (1936), in the course of a neuropsychiatric analysis of malaria, attributes the reaction entirely to idiosyncrasy for the drug, Govindaswamy (1949) in a deliberately performed study found that certain types of mentally deranged individuals as well as alcoholics (Whittingham, 1939, agrees here) and arteriosclerotics do not tolerate the drug well. Chorems and Spibopoulos (1938) have noted peculiar paralytic residuals in a small number of children. Experience in the Ceylon malaria epidemic of 1934-1935 showed, according to Fernando and Wijerama (1935), that atabrine should not be given in cases of advanced hookworm disease or where there is disturbance of renal function, Wickramasuriya (1937) agrees. Siegenbeek van Heukelom and Overbeek (1938) would have the drug used with great caution if there is jaundice or evidence of liver damage. Agranulocytosis has been reported and a few cases of hemorrhagic disturbance of the blackwater fever type (Field *et al.*, 1937, consider advanced anemia to be a contraindication), and one case of exfoliative dermatitis presumably but not certainly caused by the drug (Holton, 1938). Atabrine may apparently be safely used in any stage of pregnancy, though Wickramasuriya probably expresses the consensus when he would have it withheld in pregnancy toxemia.

The above listing seems a quite formidable array of toxic reactions but as a matter of fact most of the serious ones are of rare occurrence. Bispham (1941), of the United States Army, has studied the reported reactions in 49,681 cases in which atabrine had been given. 7915 of the cases having been seen by himself. It is true that in a large proportion of instances the drug had been

used only in prophylactic dosage, still it seems significant to me that it has caused a severe reaction only 33 times. But, however the incidence of severe reactions may compare with the same under quinine which I do not pretend to know, there seems no doubt of the fact that in routine short-course therapy the majority of individuals are disturbed much less by atabrine than by quinine.

Plasmochin—Plasmochin as now used in small dosage alone and for only a few days usually does not cause symptoms severe enough to lie of an moment—at most apparently there is some abdominal colic and slight cyanosis. But in the days when it was used in larger dosage often in combination with atabrine, there were so many serious reactions (with a number of fatalities the principal finding at autopsy being early central necrosis of the liver) that I think the indications of this type of poisoning should still be kept in the record: cyanosis of lips, face, fingers, toes; cardiac arrhythmias; gastro-intestinal pain and vomiting; pronounced disturbances in the proportions of the formed elements of the blood (lymphocytosis or leukocytosis; agranulocytosis was twice reported); jaundice, methemoglobinuria and methemoglobinemia. Since some of these reactions were likely of an allergic nature, one should be on guard. Hasselmann (1940) says he has seen one instance in which the idiosyncrasy was apparently inherited.

TREATMENT OF PERNICIOUS (MALIGNANT SUBTERTIAN) CASES

In discussing some pages back, the choice between quinine and atabrine it was stated that many men of experience now felt that quinine was a bit quicker in its action than atabrine and also that some strains of the malignant tertian organism do not apparently respond well to atabrine. It would therefore seem that upon both these counts quinine is the drug of choice at least for beginning treatment of a case of malignant tertian malaria. Dosage here should be large: i.e. the upper range as described in the section on dosage, and if the patient presents with or develops pericrucious symptoms (see the description of chalcid malaria at the beginning of this chapter) the drug should be given parenterally and at once, indeed some men inject routinely in all malignant tertian cases. Furthermore though one may argue about the preferable time in the cycle in which the drug should be given in benign tertian and quartan cases, the mandatory rule in malignant tertian cases is to give it as soon as the diagnosis is established (or before!). This section will therefore concern itself solely with methods of administering quinine and atabrine (the opinion in favor of the primary employment of quinine is by no means unanimous) by needle and by rectum.

Quinine Intramuscularly—Opinion has certainly turned away from the belief of a few years ago that intramuscular injections were to be shunned because of their painfulness and particularly their likelihood to cause abscesses, severe necroses and occasionally residual paralysis. This is in fact nowadays the preferred method of parenteral quinine introduction, apparently because we have learned how to give the injections.

Choice of Preparation—Quinine dihydrochloride used to be used but it is now recognized that its high acidity contributed toward the dangers of this procedure and it is being replaced by the simple hydrochloride rendered more soluble by the addition of urethane or antipyrine. One can easily prepare the solutions according to one of Winkel's (1940) formulae.

R	Quinine hydrochloride	gr x	0 6
	Urethane	gr v	0 3
	Water to make	℥ss	2 0
R	Quinine hydrochloride	gr x	0 6
	Antipyrine	gr v	0 3
	Water to make	℥ss	2 0

These solutions must of course be sterilized by boiling and then cooled to body temperature before use, or larger quantities may be stored in rubber capped bottles, the top being wiped thoroughly with alcohol before each withdrawal and the contents resterilized each week

It seems to me these solutions are too concentrated, i.e., 5 grains (0.3 Gm) of the quinine salt to 1 cc. Williams (1940) places 5 grains in 5 cc., and Fernan Nunez tells me he found years ago that if the rule of 1 grain to 1 cc. was followed he had very few abscesses even when using the dihydrochloride salt. I would therefore suggest the following formula

R	Quinine hydrochloride	gr x	0 6
	Urethane		
	or		
	Antipyrine	gr v	0 3
	Water to make	℥ss	10 0
	Label: Sterilize by boiling and when cool inject 1 cc. for each 1 grain (0.6) of quinine desired		

Technic of Intramuscular Injection—The patient lies on his side and fully flexes the uppermost leg and then, with full aseptic precautions as to syringe needle and preparation of skin the injection is made deeply at a point about 2½ to 3 inches below and behind the anterior superior iliac spine (in young children, Williams selects a point ½ to 1 inch below the crest of the ilium on the posterolateral aspect of the buttock, advances the needle until bone is encountered, withdraws very slightly and injects). It is important that the needle without any solution in it be introduced first and then the syringe attached and at the conclusion the quinine syringe must be replaced with one containing a little air or sterile water to be injected to clear the needle of solution before it is withdrawn. These injections must be made slowly and at their conclusion the area is to be gently massaged for ten minutes.

Dosage—The same amount of drug and at the same intervals may be employed intramuscularly as by mouth but it is often found that after the first injection (10 to even 15 grains [0.6 to 1.0 Gm]) may seem indicated in some fulminating cases) the subsequent doses can be considerably reduced. Of course the objective is to save the patient's life and then to get him on to oral administration, this is usually accomplished in a few days.

Manson Bahr (1940) says that the bowels should be freely opened with salts which enable the quinine to act more efficiently, 'especially when given intramuscularly'—I do not understand this but that is what he says.

Quinine Intravenously—It is nowadays the consensus that this method should be employed only in patients who seem in extremis because the syncopal reaction, possibly due to the effect upon the myocardium of rapidly liberated toxins is often very serious (interestingly, Hall 1941, says that in Nigeria the natives do not experience this reaction). The same preparation and dosage may be used as in the intramuscular method but the injection

must be given extremely slowly—at the rate of not more than 1 cc per minute—and epinephrine (adrenalin) solution should be at hand in case of collapse. The boldest intravenous therapy I have ever heard of is that of Most and Jolliffe (1910), who have given 10 grains of quinine every three to four hours for at least twenty-four hours to some of their cases of severe malarial subtertian infections in drug addicts in New York.

Quinine by Rectum—For the adult, 30 grains (2 Gm) of the dihydrochloride may be dissolved in 1 quart (1000 cc) of normal saline and given by rectal drip during twenty-four hours, 2 ounces (50 Gm) of dextrose added to this will enable one to supply specific drug nourishment fluid and salt to a patient dehydrated by continuous vomiting. For the preparation of a retention ecema if a soluble salt of quinine is not available and the sulfate must be used. Manson Bahr (1936) directs that the drug be dissolved with the aid of tartaric acid to avoid making the solution irritant, hydrochloric acid will necessitate such dilution as to make it difficult for the ecema to be retained. In children having convulsions which is the counterpart of the cerebral form of pernicious malaria in the adult, he advises heroic dosage: 5 grains (0.3 Gm) in a one-year-old child, followed by half this quantity every hour until convulsions cease. In these children the buttocks will often have to be pressed together to ensure retention, normal saline or thin mucilage are better solvents than plain water.

Atabrine Intramuscularly and Intravenously—Ampules are commercially available containing 3 grains (0.2 Gm) atabrine dihydrochloride, accompanied by a 10-cc ampule of distilled water. It is recommended that for intravenous use all the powder be dissolved in the water but only half the solution (a dose of 0.1 Gm) be given an adult and only one fourth the solution (a dose of 0.05 Gm) be given children up to eight years of age. It is nowadays felt best not to give more than three such doses in twenty-four hours. For intramuscular use it is preferred by the manufacturers that the contents of the ampule (0.2 Gm) be dissolved in only 7 cc of water. The intramuscular dose is usually the same as the oral or intravenous dose (0.1 Gm for the adult) but in extreme cases may be doubled or possibly even trebled. The intramuscular route is usually preferred, Vard (1935) found atabrine in the urine within two hours of its intramuscular injection and more delicate tests would probably detect it there much earlier.

GENERAL CARE, NURSING, DIET, AND A FEW SPECIAL MEASURES

It seems to me very important to emphasize to practitioners in the temperate zones where malaria is likely to be increasingly seen under present world conditions that this is a serious disease and not to be treated lightly merely because it bears the unimpressive soubriquet 'chills and fever'. During his first paroxysm of one of the intermittent types the patient will put himself very miserably to bed but the point is that he should be required to remain there until adequate use of one of the specific drugs has assured that the acute attack is over, he may be allowed up during the period of after-treatment with plasmoquine. Every effort should be made to try to mitigate his discomfort during the chill stage and when he is sweating the bedclothes and his night clothing need frequent changing. The ordinary analgesic and antipyretic drugs are perhaps hardly worth using during the fevered stage but if

hyperpyrexia develops the cold pack must be employed, Manson Bahr (1040) says it is a good rule to put the patient in the pack when the axillary temperature reaches 100°F (about 41°C) and remove when the rectal temperature is 102°F (about 39°C). During the acute attack of benign tertian or quartan the diet presents no problem for the patient even if not vomiting is unlikely to desire more than the lightest food, return to full diet after the paroxysm may be rapid.

In the severe vomiting of the bilious type of pernicious malaria, Fernan Nunez considers that the use of such supposed gastric sedatives as chloroform water, chloral hydrate and tincture of iodine merely constitutes unnecessary torturing of the weakened sufferer and may even add to his depression morphine sulfate should be given hypodermically, $\frac{1}{4}$ to $\frac{1}{2}$ gram (0.008-0.015 Gm). He also considers that the use of the stomach tube is contraindicated. Sinton, in his vast experience, found that vomiting may be remarkably well controlled by the oral administration of 20 minims (1.3 cc) of epinephrine (adrenalin) solution. To combat *dehydration* large quantities of physiologic saline solution, preferably with the addition of 5 per cent of dextrose, will have to be given, sometimes *blood transfusion* also seems indicated. Lipscomb (1930), following Sinton, advocates the use of *allahs* in the hope of preventing blocking of the tubules of the kidneys by liberated blood pigment. If an attack of the *cerebral* type is threatening, Manson Bahr (1040) applies ice bags to head and heat to the feet. It is said that the inhalation of amyl nitrite may make the parasites more accessible to the specific drugs through dilatation of the vessels but I much doubt the wisdom of such therapy. In a recent case Fawcitt and Walters (1041) followed an intravenous quinine injection with the intravenous administration of pooled serum (400 cc, dripped at the rate of 40 to 60 drops per minute), with Manson Bahr, on whose service the case was seen, they thought that the excellent result was possibly due to dilution and perhaps to some extent neutralization of the circulating malaria toxin and also to minimization of quinine shock sometimes sustained by extremely debilitated patients. If there is no remission of *coma* in eight hours it is sometimes the practice to withdraw 50 cc of spinal fluid, under such circumstances. Most and Jolliffe (1040) simultaneously give intravenously 50 cc of 50 per cent dextrose solution containing 1 cc of 1 to 10,000 epinephrine (adrenalin) solution. They say they repeat in six hours if no improvement has been obtained and feel that occasionally dramatic recoveries are ascribable to this procedure.

The observations of a number of Continental workers (see Lotze, and Gerdjikoff, in Bibliography) indicate that in malaria there may develop a considerable vitamin C deficit, both through loss and poor absorption, for methods of administering *ascorbic acid*, see Index.

Some years ago, Lio made a trial of *autohemotherapy*. He drew 10 cc of blood from a vein and reinjected it, without added citrate, intramuscularly into the buttock, giving from four to seven injections on alternate days. In his small series of cases the results were quite promising. Aractingi (1037) tried the treatment on 100 old infections, mostly benign tertians, withdrawing and injecting the blood during fever free intervals and giving each patient 4 injections at intervals of three to five days. In 80 of the cases fever ceased after the third injection and they remained well during a subsequent observation period of seven months, in 15 cases fever ceased after the fourth injection.

but there was a mild return twenty days later, in 5 cases only did he consider no benefit was derived. Lorando and Soteriades (1937) have also had good success with the injection into malarious children of immune parental whole blood. Many tropical practitioners feel that in the regions of heaviest infection with malaria there is also nearly always sufficient infestation with worms to warrant the use of a *vermifuge* as soon as the patient's condition warrants it. Whether *alcohol* should be forbidden the patient entirely between attacks is a moot point, but it is agreed that *excesses* of every description should be avoided, particularly *cold baths* (except during the hyperpyrexial attack) and *exposure to strong sunlight* and *ultraviolet lamps*. Fernán Núñez found relapses especially frequent among those engaged in *hot work*—cooks, firemen, laundry workers, etc. Only the most imperative *surgery* should be performed upon a malarious individual since operation is particularly prone to produce relapse.

MISCELLANY OF OTHER DRUGS

Quinidine—It has been known for many years that several of the other alkaloids obtainable from cinchona bark have antimalarial value, of these, cinchonine and cinchonidine, hydroquinine, hydrocinchonine and hydrocinchonidine have not attained much practical importance as yet, but quinidine sulfate is beginning to be quite considerably used in the same dosage and with the same results as the salts of quinine itself. Indeed, Sanders, reporting on a cooperative study of the drug with other physicians in Louisiana in 1340 cases in 1936 and 1138 cases in 1938, thought that the weight of evidence was slightly in favor of quinidine when it was compared with quinine in short course therapy. The fact of quinidine's use in paroxysmal tachycardia has caused some physicians to fear that it might be a dangerous heart depressant, but this is not borne out in Sanders' experience. A few only of his patients complained of weakness shortly after taking the drug but this did not recur when they were asked to stay in bed for an hour after taking it. Some complained of nausea but this may have been attributable to the malaria as well. There were a few instances of idiosyncrasy as with quinine but the drug has also been used satisfactorily to replace quinine in instances of idiosyncrasy to the latter. In ordinary, routine therapy quinidine seemed to cause less tinnitus and nervousness than the classical drug. In 1935, Sanders reported a series of 32 pregnant women in all stages from the first to the ninth month, who were treated with quinidine without any ill effects upon either mother or infant.

Totaquina—Various cinchona febrifuges have been used during the years in trying to supply a relatively cheap form of antimalarial drug to pauper native populations. The one which has found greatest acceptance is "totaquina," a febrifuge standardized to contain variously 50 to 78 per cent of crystallizable alkaloids. According to Manson Bahr (1940), Indian totaquina contains 7.4 per cent quinine and 22.8 per cent quinidine, and the Javanese product 11.5 per cent quinine and 5 per cent quinidine. In Field's (1934) study there were 417 totaquina treated and 181 quinine-treated patients, he found clinical signs disappearing with equal rapidity but parasite disappearance lagging a little with the totaquina. For average Asiatics he thought 20 grains (1.3 Gm.) a day in capsules the best dosage. There have been numerous reports all indicating that the drug has nearly if not quite as great value as

quinine—some observers indeed claim for it a greater value, as witness the following Wijerama (1939) treated 95 patients with totaquina and 132 with quinine bisulfate, some receiving 15 grains (1.0 Gm) and some 20 grains (1.3 Gm) of either drug daily, there were 127 malignant subtertian, 59 benign tertian, 10 quartan and 31 mixed infections. Totaquina proved the more effective in stabilizing temperature, causing the disappearance of parasites, and inhibiting the formation of gametocytes in all three types of the disease.

Organic Arsenicals—From time to time through the years there has been advocacy of these drugs in very much the same way in which they are used in syphilis. Arsphenamine, then neoarsphenamine and sulfarsphenamine, then acetarsone (stovarsol), and now mapharsen (Goldman, 1938) have had their day. Fernan Nunez felt that they were alone specific in benign tertian cases and much facilitated the action of quinine in malignant subtertian cases and were of value in any case in which proper response to quinine was not being obtained, he also thought them to be of great tonic value. Lipscomb (1939) thinks that an injection of one of these drugs will drive the organisms into the circulation, which he apparently feels is essential for their destruction. Manson Bahr (1940) admits some effect in benign tertian but none in malignant tertian or quartan cases, and he says that a course of an organic arsenical in the apyretic periods will not prevent ordinary relapses, tonic effect he admits in some cases—especially if the patient also has syphilis.

Tartar Emetic (Antimony Potassium Tartrate)—In 13 of 14 adult patients with malignant subtertian infections that had resisted quinine, plasmochin and atabrine, DeNunno (1935) induced recovery by the intravenous injection of tartar emetic, the fourteenth patient discontinued treatment because of intolerance for the drug. Dosage was similar to that in kala azar. Garra (1940) also thought highly of the drug as used by him in a small series of cases in Italian East Africa.

Methenamine (Urotropin)—Umansky (1931) gave this drug intravenously in the cerebral type of attack. His belief is that the "purification" of the capillaries in the brain is brought about by the fixing power of the formaldehyde produced from the methenamine, an explanation which completely lacks experimental support and is probably untrue, but the important point is that Umansky claims that all the symptoms of the comatose or convulsive states disappeared in three to six hours after a single injection of 3 cc. of a 40 per cent solution of the drug (sterilized by boiling) in his 10 cases. Pyrexia, presence of the organisms in the blood, etc., were not affected.

Other Drugs—*Methylthionine chloride (methylene blue)* used to be resorted to in patients who could not tolerate quinine, but since we have atabrine, this drug has fallen completely into the discard. Vanadium is being tried in South America but there is as yet little to report, Pereira (1939) failed in his 2 cases. Watson (1939) reports favorably upon *bismuth violet* injections but I think we must reserve opinion until his results have been confirmed. The Italians are experimenting with *manganese iodo mercurate*, but there is nothing which I feel justified in reporting here as yet. Cole et al (1940) have satisfactorily employed *bismuth* compounds, such as are employed in syphilis, for the purpose of temporarily checking the fever in the malaria therapy of paresis, I do not know of any thorough study of this metal in naturally acquired malaria. It seems to me unnecessary to review the literature of the *sulfonamides* here for these drugs have failed to be consistently effective in

malaria, even in the latest report, that of Coggeshall *et al* (1941), who studied sulfadiazine and promin in naturally acquired infections in Panama it is emphasized that there are no reasons for preferring these agents to quinine or atabrine

TREATMENT OF CHRONIC MALARIA

As I said earlier in this section, there is need for a clear delineation of chronic malaria (what a fine task for some intelligent young man in the South to set himself to!) For the present one can only say that in addition to the rather easily recognized state of malarial cachexia there is a large group of individuals in malarious regions who are frequently sick in an ill-defined way that seems undoubtedly related to an earlier attack of malaria. In the South many individuals who have long ago forgotten the "chills and fever" they had in their youth dose themselves periodically with calomel and salts—perhaps they would do much better to take quinine or atabrine at these times? Of course anemia must be vigorously combated and in many parts of the world malnutrition, malaria, and helminthiasis are an almost invariable triad. Most physicians in the tropics recognize the advisability of a change of climate, the patient's resistance being increased during the sojourn in a temperate region while the parasite is dying out in his blood, since the latter occurrence requires a long time, however, this relief measure is practicable for only the relatively few who are more or less economically independent. High altitudes are generally preferred but recuperation actually takes place just as well in any bracing northern climate.

Anti-relapse Treatment—In discussing the treatment of acute malaria the accepted methods of using quinine, atabrine and plasmochin in attempting to reduce the number of relapses were described, but mention should be made here of the "old fashioned" method, which may indeed have much to recommend it, of continuing to use quinine or atabrine for short periods at frequent intervals during the season of expected relapses. The two schemes most frequently employed are (a) to take full doses of one of the drugs on two consecutive days each week, and (b) one-third to one-half doses for one week each month. In Russia a few years ago (Rachina *et al*, 1937) a study was made of this method in 4000 persons, of whom an adequate proportion were used as controls, who had suffered from benign tertian malaria in the preceding year and in whom relapses were to be expected in the succeeding spring. They gave three- to five-day courses of treatment with two-thirds full therapeutic dosage, three such courses with ten-day intervals. The conclusion was that if treatment is begun a few days before the wave of relapses is expected it can prevent the relapses—which amounts in fact merely to beginning treatment in time enough to prevent the appearance of symptoms.

Ascoli (Epinephrine) Treatment—A number of years ago Dominici introduced the intravenous use of epinephrine (adrenalin) in chronic cases with a considerable degree of splenomegaly and anemia, the purpose being to force large numbers of erythrocytes out of the splenic sinuses into the peripheral circulation and at the same time decrease the size of the spleen. The method was popularized by Ascoli, in 1937. It consists in giving daily intravenous injections of the drug beginning with 1/100 mg (1 cc of familiar 1:1000 solution contains 1 mg), increasing to 1/90 mg the next day, 1/80 mg the next, and so on until 1/10 mg is reached, this last dose is repeated daily for

twenty days. It is said that the spleen is almost invariably much reduced in size by this treatment and that the general well being of the patient is greatly improved. Some men give quinine or atabrine during the course, some after it and some not at all routinely, patients previously recalcitrant to the specific drugs are said to respond to them after the Ascoli treatment. When the treatment is used shortly after recovery from an acute attack it is said that subsequent relapses are remarkably mild (Pizzillo, 1938) and do not require the use of specific drugs. The reports have been almost exclusively Italian; one would like to see a thorough study of the method elsewhere.

DRUG PROPHYLAXIS

The attempts at prevention of the disease that might logically be made in the current state of our knowledge are the following *Mass Treatment*—By this I mean making monthly parasite surveys of an area and treating all the positives with drugs in the hope of greatly reducing transmission in the area. It does not succeed, as was shown conclusively by Clark and Komp in their thoroughgoing ten year study (1931-1941) in Panama. They did not even succeed in preventing epidemics when unusual numbers of mosquitoes were present, but they were successful in reducing cases of severe clinical malaria in the region almost to the vanishing point. *Plasmochin and Certuna*—One would think that the administration of one or other of these drugs of demonstrated gametocidal properties to the entire population of a given malarious region would practically prevent mosquito transmission of the disease in that region, and it is faintly possible that it would—but I cannot conceive of any public health official of sound mind undertaking such a gargantuan project. Even reduced to theoretically attainable proportions, i. e., the administration of the drug to demonstrated carriers only, the method is impracticable. Earle and Perez' (1930) study in Puerto Rico showed this, for three years from 30 to 40 children (the most important gametocyte carriers) in an endemic center were kept under continuous observation, the malaria parasites being counted once a week or more frequently when fever was present or numerous gametocytes were found—the only admissible conclusion from their work was that there is no way of predicting the presence of gametocytes in the blood stream and, therefore, that in order to keep check upon those who are and those who are not carriers at a given moment in any region blood smears would have to be made of the entire population at impossibly frequent intervals.

Causal Prophylaxis—There is not as yet available any agent which will effect true causal prophylaxis by destroying the sporozoites injected by the mosquito—and that is that!

'Clinical' Prophylaxis—What remains is simply the attempt, under the title of clinical (in the sense of practical) prophylaxis, to maintain sufficient concentration of the specific drugs, quinine or atabrine, in infected individuals so that the asexual forms of the parasites which they harbor cannot cause severe symptoms and the sexual forms are reduced sufficiently that infectiousness for mosquitoes is much decreased. This subject must be discussed under two heads, mass prophylaxis and individual prophylaxis.

Mass Prophylaxis—It is important to understand that quinine has always been a valuable prophylactic agent and that the low repute in which

it is generally held merely reflects the fact that in most mass experiments the drug has only been issued to the populace and nothing else done about it. Where its use is rigidly controlled it succeeds. Witness the experience of the French Army in Greece in World War I, as told by the well known malarialogists the brothers Sergeant (1932). When the army disembarked at Salonika in the autumn of 1915, Ross, Laveran and others who could speak with authority gave clear warning that malaria would be experienced unless timely precautions were taken. But nothing was done, and the result was that in the spring of 1916 there were some 60,000 cases of malaria in a force of about 115,000 men, and in the autumn not more than 20,000 men were in the lines. General Sarrail was obliged to report to his government that his army was immobilized in hospital. Then the malarialogists were allowed to go into action and a quick survey showed that the only hope lay in the use of rigid prophylaxis with quinine, which was the only drug available in those days. So it was given to everyone not as a medicine but as a ration, refusal to take it was regarded as refusal to obey orders in the face of the enemy, and when a urine test showed that the body did not contain an adequate amount of quinine the responsible officer, not the private soldier, was punished. The result was success and the army was saved. The opposing German army, employing no special antimalaria measures, served as a control, malaria mounted in it during 1917, while it rapidly went down in the Allied forces. Mühlens (1939) has reviewed that campaign from the German standpoint and says they failed with quinine prophylaxis because they only put the drug 'in the soldier's hand and not in his mouth'. In reviewing in late 1939 the necessary precautions the British would have to take in this current war, both James and Wenyon stated that quinine succeeds in preventing clinical malaria in mass operations if its taking is enforced. Castellani (1939) also leaves no doubt about its effectiveness in holding down malaria in the Italian campaign in Ethiopia a few years ago, however Manson-Bahr (1941) has cast very considerable doubt upon the admissibility of the Italian statistics.

In recent years there have appeared throughout the malaria world numerous reports of the successful use of atabrine in the prevention of the disease. In our own country perhaps outstanding among these have been those of Seekinger (1936), Wiachester (1938), Hill and Goodwin (1938), and Bispham (1938). Typically, all persons found harboring malaria parasites in the selected region are given a preliminary five-day course of atabrine and then two groups designated as the prophylactic and the control groups are formed; thereafter the prophylactic group is given atabrine in suitable dosage throughout the period of mosquito prevalence and the other group receives no medication during this period. During the malaria season weekly check-ups are made in each group to determine the presence of clinical malaria and blood smears are taken from every case showing either suspicious symptoms or giving a suggestive history. Excellent results are reported but there are no studies available as yet comparable to the above-cited ones in which quinine was used. Of the several reports available in which attempt was made to compare quinine and atabrine in rigidly controlled mass prophylactic experiments, it seems to me that the two most definitive are that of Field *et al.* (1937) in Malaya and Lamprell (1940) in India. In both these studies the groups taking each drug were of adequate size and the control

group was as satisfactory as can be arranged under field conditions. In each there was marked reduction in clinical malaria while the drugs were being taken, the reduction being greater in the atabrine groups, but upon cessation of the experiment there was an increase in clinical malaria in the treated groups above the control groups, and this increase was greatest in those who had received atabrine.

Summarizing the subject of mass drug prophylaxis in malaria one may say that (a) both quinine and atabrine if faithfully taken will markedly reduce the incidence of frank clinical malaria, (b) atabrine seems to be somewhat more effective in this than quinine, (c) upon terminating the use of the drugs the incidence of malaria in those who had taken them rises higher than in comparable untreated groups, and (d) in this post-treatment rise those who had taken atabrine predominate.

Individual Prophylaxis—Surgeon General Parran of the U S P H S, has said that no major military operations in the tropics of our own western hemisphere are possible without quinine or atabrine, apparently leaving it wide open to our military and naval forces to make thorough studies of both drugs. The following is but an attempt to outline the present status of the matter for the private practitioner.

Choice of Drug—Most residents of tropical countries long ago ceased to have any doubt of the efficacy of quinine. Manson-Bahr (1940) says that in prophylactic dosage it does not interfere with menstruation, conception or pregnancy—it is well established that atabrine does not either. However, as reports stand at present atabrine seems to have the advantage over quinine since it is apparently somewhat more effective and certainly easier to take (no ringing in the ears, nervousness, etc., and the gastro intestinal disturbances it occasionally causes are usually not severe). But the patient's skin will take on a bronzed hue from the ingestion of the drug, and when he ceases taking it—whether he is still in or has come out of the malarial region—he is more likely to develop a delayed attack than if he had taken quinine. Atabrine is also usually considerably more expensive than quinine.

Dosage—The League of Nations Malaria Commission stated the preferred dosage to be 6 grains (0.4 Gm) of quinine sulfate daily, or 3 grains (0.2 Gm) of atabrine dihydrochloride on two days of each week. Some individuals take the drug night and morning in half doses and some all in one dose, atabrine should be taken on nonconsecutive days (for example on each Monday and Thursday). Of course there are variants from this dosage. Many people in the tropics take 10 grains (0.6 Gm) of quinine daily (Castellani employed this dosage in the campaign in Ethiopia), and Simmons (1938) says that in the Canal Zone men are given 15 grains (1.0 Gm) daily during periods of unusual exposure outside the sanitized areas. Hall (1941) says that the Europeans in Nigeria who take prophylactic quinine, while not having fever often suffer from general lassitude, a "heavy" head, and occasional headaches, he says an intramuscular injection of 5 grains (0.3 Gm) of quinine is usually sufficient to clear up this muggy state. Reducing prophylactic dosage for children about as therapeutic dosage is reduced, the following would probably be satisfactory if the adult dosage is taken as 6 grains: under one year $\frac{1}{2}$ grain (0.03 Gm), first and second years, 1 grain (0.06 Gm), third and fourth years, 2 grains (0.12 Gm), fifth to eighth years, 3 to 4 grains (0.2 to 0.25 Gm), ninth year and up, 6 grains (0.4 Gm). With

regard to atabrine I think that a number of well-controlled studies, such as the well known one of Mosna and Canalis (1937), have established the superiority of the 0.2 Gm dose twice weekly, though some men are undoubtedly getting good results with the originally recommended 0.05 Gm daily. Hill and Goodwin (1938) used 0.1 Gm three times weekly. For an adult dosage of 0.2 Gm, Manson Bahr (1940) would give 0.05 Gm up to two years, 0.075 Gm. from two to four years, 0.1 Gm from five to eight years and the adult dose above eight years.

Length of Course—Either drug must be taken through the period of transmission of the disease—for example, from April through October in parts of our South, and the year round in some tropical regions. No advantage is gained by an individual's beginning a course before he enters the malarial region (though he must begin at once upon arrival), but many men of experience are now stressing the advantage of persisting in the course for a month to six weeks after the transmission season is over or after leaving the region—such men as Mühlens and Manson Bahr insist upon this.

"Blanket" Treatment After Prophylaxis—It has many times been stated in the past that the individual leaving a malarious region should put himself through a full course of therapy with full dosage for one week as soon as he is out of the region, during the current war Manson Bahr (1940) is insisting that all persons returning from endemic areas take 0.3 Gm of atabrine daily for a full week (even though a drug has been used prophylactically during all the period of tropical residence) and reports that results are amply justifying this measure.

Danger from Long Employment of the Drugs—The reader is referred to the discussion of toxicities under the therapy of acute malaria for indications of what might be expected. How much permanent damage has been done through the years by quinine prophylaxis is unknown to me but surely the amount cannot be very great else one would read or hear of or see cases at intervals, that malaria itself causes neurological sequelae must not be overlooked in assessing damage allegedly due to the drug. Of permanent residuals of atabrine ingestion there seem to have been none reported as yet, Junge (1939) reports 20 Europeans in Liberia who are said to have taken the drug continuously for seven years without harm save of course a constantly stained skin.

MEASLES AND GERMAN MEASLES

(Rubeola, Morbilli, Rubella, Rotheln)

Measles is an acute infectious disease of whose victims more than 95 per cent are under fifteen and more than 60 per cent under five years of age. It is so highly contagious that most children fairly intimately exposed contract the disease, with the exception of infants under three months even the latter are not immune if the mother has not had the disease and indeed may be born with it if the mother is ill of it at the time of her labor. Adults also are susceptible, as was distressingly shown during World War I when severe epidemics prevailed in the American mobilization camps among recruits from rural districts who had not been immunized through having an

attack in their childhood. The disease is endemic in large cities and often becomes epidemic in the winter months. In New York City in recent even numbered years the cases have averaged about 35 000, while in the odd numbered years there have been only about 8000 cases. During the current war, and probably due to the closing of schools and the evacuation of large numbers of children, the regular biennial cycle of epidemics has been broken in London, and in Manchester and Birmingham the epidemics have been delayed and mild. The incubation period may be as short as seven days but is probably rarely longer than fifteen days except in individuals who have been given one of the types of protective serum. The early symptoms are catarrhal inflammation of the eyes, nose and upper respiratory tract, fever and the malaise, chilliness, loss of appetite, vomiting, etc., which characterize many of the acute infectious diseases in their incipency. Then, on about the fourth day and often after the fever has entirely disappeared, the typical dusky, crescentic, blotchy, maculopapular rash appears, principally on the face and back, and is accompanied by a recrudescence of all the symptoms. Early in the attack there is frequently a reduction in the number of circulating lymphocytes, a helpful diagnostic sign, Koplik's spots (an eruption on the buccal mucous membrane) often appear too late to assist toward an early diagnosis. After the eruption reaches its height, which occurs in from thirty six hours to three days, the patient begins rapidly to improve, though the skin usually retains for a week or more a brownish stain where the eruption has faded. The branny desquamation is complete within ten days.

Measles respects neither climate nor race, but it was apparently not differentiated by the classical ancients. The first clear description is that of Rhazes (860-932 A.D.), during the period of the Mohammedan ascendancy in medicine. In later times it was confused with scarlet fever, but Sydenham clearly differentiated the two diseases in the seventeenth century. Due to its many complications—of which bronchopneumonia, laryngitis with edema and enteritis are the most serious—measles mortality was formerly very high (6 per cent in good hygienic and nutritional surroundings, 15 per cent in institutions, as high as 35 per cent in harrack epidemics), but in recent years the death rate has been steadily declining. Complicating encephalitis and other clinical types of nervous sequelae do not very much increase the total mortality because the cases, though often fatal, are rare though the incidence has seemed to be increasing in recent years. Perhaps there is some relationship between measles and appendicitis (Hudson and Krakower, 1936), at any rate when the latter is diagnosed, operation is apparently indicated though measles is present. Cases with a bullous or pemphigoid tendency, and also instances of noma or cancrum oris as a complication, are fortunately extremely rare.

Claims have been made by several workers that they have identified the causative organism in the form of a visible coccus, but generally satisfactory substantiation is lacking. Certain inclusion bodies, differentially stained with nigrosin, have also been found in smears from the nose and from Koplik's spots. However, it is still the consensus among bacteriologists that the etiologic agent is a filtrable virus. The frequent finding of certain giant cells in the lymphatic tissues during the prodromal stages is still without explanation. The possibility of a second attack of measles is admitted but such an occurrence is certainly one of the greatest of medical rarities.

German Measles (Rubella, Rotheln)—This highly contagious disease resembles measles and scarlet fever but is distinct from both. It, too, is probably caused by a filtrable virus present in the nasal secretions. The differential points in its diagnosis will not be gone into here, suffice it to say that an outstanding feature of the disease is an adenitis of the mastoid, occipital, cervical, and often the inguinal and axillary glands. An attack of measles seems to predispose to infection with German measles. Complications are rare and usually not severe.

THERAPY

General and Nursing Care—The general treatment of measles is that of grippé. Especial care *must* be taken to prevent cross infection, as death rides jauntily in the wake of complications here. Complete isolation with the nurse is the ideal to be approximated as closely as possible. Keep the patient warm in an airy room, protected from direct drafts. Admit all the sunlight possible, but protect the eyes, by the use of either dark glasses or improvised screens, and irrigate them frequently with boric acid solution, the application of petrolatum (vaselin) may prevent adhesions of the lids. Placing the child for a few minutes in a warm pack will often 'bring out' a delayed rash. The irritation of the skin which is sometimes annoying during the period of the rash will usually yield to sponging with a dilute sodium bicarbonate solution, if excessive, 1 per cent phenol may be substituted. The daily bath should be continued during the desquamation period, but it is well to follow it at this time with an application of petrolatum. Petrolatum to soften crusts and sprays (see Common Cold) for whatever they may be worth, are available for keeping the nose clean and comfortable, but their application in a way that will suit the young patient will tax the ingenuity of any nurse.

Watch the ears, watch the throat, watch the temperature and respirations in a word, *watch for complications*.

Sulfonamides—Several British physicians have tried the earlier members of this series, but the results, other than the effect upon complications of streptococcal origin, were not striking. Anderson (1930) felt that they had a place in the treatment of measles in open wards where the chances of cross infection are great.

Amidopyrine—In 1924, Loewenthal published an account of the use of amidopyrine (pyramidon), and a number of physicians have since reported its successful use. Ronaldson and Collier (1930) surveyed their results in 150 cases, which they carefully point out were treated in a year in which the measles prevalent in London was milder than usual. The dosage adopted was 1 gram (0.06 Gm) for every year of age, with a maximum of 5 grains (0.3 Gm), administered in aqueous solution of 1 grain to the draehm (0.06 Gm to 4 cc) every four hours until the temperature had settled. In addition to the antipyretic effect, the tendency to bronchopneumonia and some of the other complications was lessened, but not laryngitis and enteritis. On the other hand Attlee's patients given the drug were more uncomfortable than those not so treated, and in Borovsky and Steigmann's (1933) study of 104 cases, in which alternate patients were given the drug, they found nothing that would indicate a special therapeutic value for it. It certainly seems to me that one should now be chary of the use of amidopyrine in view of its potential toxicity (see Aggranulocytosis).

PROPHYLAXIS, *i. e.*, PREVENTION AND MODIFICATION

Measles spreads so rapidly because it is most infectious in the period prior to the appearance of the eruption. After the eruption has reached its height the contagiousness is practically nil, indeed, many municipal health departments permit the release of a child from quarantine five days after this time, provided, of course, that it is well and that the acute rash has disappeared. The bounden duty of physicians toward the individual and the community is to quarantine all susceptible exposed persons for a period of two weeks from the date of exposure, this is the practice of most departments of health, but Hobson (1938), in England, has been maintaining for a number of years that three weeks is a safer period, for even in individuals who had not received any sort of protective treatment he has seen first prodromal symptoms on the fifteenth day after exposure and no rash until five days later.

In recent years it has become possible to prevent the occurrence of measles, or if preferred to modify its severity only, *i. e.*, to "attenuate" the attack. In what follows I shall attempt briefly to describe the agents used and their practical employment.

Stored Convalescent Serum—About the turn of the twentieth century, Weissbecker is said to have successfully employed large amounts of serum from convalescents in the treatment of several cases of measles in which the symptoms were just beginning, but Nicolle and Conseil (1918) were the first to publish on the method. Since that time the efficacy of convalescent serum in preventing or modifying the disease has been fully established by many qualified observers. It may be safely collected five days after defervescence of the fever. At the Milwaukee Serum Center (Hardgrove, 1941) it is obtained preferably from the end of the second week to the end of the second month, but the Council on Pharmacy and Chemistry (1941) says that it may be collected up to six months after the onset of the attack. Council accepted serum may now be obtained from the Milwaukee Serum Center, Samuel Deutsch Convalescent Serum Center of Michael Reese Hospital in Chicago, Children's Hospital Convalescent Serum Center in Los Angeles and the Serum Exchange of the Children's Hospital in Philadelphia. The potencies of various batches of serum probably vary widely at present and will continue to do so until some method of titrating and standardizing is developed. Nor do we know precisely its rate of deterioration, at the Milwaukee Serum Center it is felt that dosage had better be increased if the serum has been in storage more than a year.

Convalescent serum does not cause reactions nor sensitize the patient to subsequent injections.

Stored Adult Serum—The pooled serum of adults or of older children is often used because of the difficulty of obtaining sufficient serum of recent convalescents. Such "normal" serum is much less potent than convalescent serum and must therefore be used in greater dosage. Burnet (1935) has shown that the serum of adults up to fifty years of age is just as potent as that of younger persons but that all such sera lose about 40 per cent of their value upon six months' storage though retaining this lowered value for about another eighteen months. Experience has shown that repeated and direct exposure makes for high potency even without the history of an attack of measles, doctors and nurses actively engaged in work in infectious disease wards make good donors, for example. Both Lichtenstein (1931) and McGuinn

ness *et al* (1937) have described methods for drying these sera and redissolving them just before use but not much general experience has been had with these methods

Adult serum, like convalescent serum, does not cause any reactions nor sensitize the patient to subsequent injections

Methods of Employing Convalescent Serum, Adult Serum, and Immune Globulin—This subject falls naturally into several parts, as follows *Prevention or attenuation?* Should one attempt to prevent the occurrence of measles in contacts or merely attempt to modify its severity and lessen the likelihood of complications? I think that Schwartz (1941), of Milwaukee, expresses the consensus when he says that it often seems judicious to attempt to prevent it entirely in the younger children and to modify it only in older ones. In effect such practice (i.e., complete prevention) merely amounts to postponing the age at which the individual will have measles since immunity conferred by one of these agents lasts only two to six weeks. Upon the other hand the use of the preparation in such way as to permit the patient to have only a light attack of the disease apparently confers as long lasting immunity as on unmodified attack. But since the most deadly age period by far for measles is under three years, many men make it a rule always to attempt complete protection in this group. Children of any age acutely or chronically ill with any other disease at the time of exposure to measles are also prone to have severe attacks, and in them also full protection should be attempted. Finally, when measles appears in a hospital ward it is the usual custom completely to protect all children even remotely exposed, the purpose here being not only to safeguard the children but also to prevent serious disruption of the hospital service through a protracted period of quarantine. In other individuals—children or adults—not in either of the three above classes, it seems to be the consensus that the use of these preparations in such way as will permit the occurrence of a mild attack, rarely accompanied by complications but succeeded by lasting immunity, is the preferred method.

Should all contacts be immunized? In other words, is the mere fact of exposure enough to warrant an attempt being made to attenuate the expected attack if the children are beyond infancy and healthy? Certainly most physicians having a clientele able to afford convalescent serum will answer "yes," for no reactions follow this serum, adult serum, too, is not followed by reactions and many men routinely employ it whenever a child has been exposed. But, because of the reactions, I see no evidence of eagerness in the literature or among my friends to recommend the use of immune globulin routinely in all contacts. For one thing there are many degrees of contact, Karelitz and his associates (1935-1938) have been stressing this point particularly. They show that exposures during casual contacts at play, in buses, schools, at parties, etc., are not at all comparable in their likelihood to eventuate in contraction of the disease to exposures in the home. They say also that exposure in the home will be light if the hygienic situation is good and the patient is separated from other children of the family at once on suspicion of the disease, and also that it will be very heavy if the hygiene is poor and all the children remain together during the development of the cases. So therefore, if one cannot use either of the sera and must employ immune globulin, I should think that the likelihood of the contact having been really a serious one might have to be weighed in some individual cases. Hobson (1933), as a result of his experience

in several epidemics with excellent environmental hygiene and nursing precautions in preparatory schools for boys in England, goes the whole way and says that healthy susceptible individuals should be permitted to experience a normal attack of measles after exposure even though convalescent serum is available. I doubt that many in the United States are in agreement with him.

Choice of Agent—Pooled adult serum does not cause reactions and it seems to me that it should be used more than it has been because there is plenty of it available and the fact that it has to be used in dosage three or four times that of convalescent serum is really not a serious objection. However, the choice is usually considered to lie between convalescent serum and immune globulin: the former not causing reactions but being expensive and not everywhere available, the latter everywhere available but quite prone to cause reactions. Regarding the comparative efficacy of these two agents, the most satisfactory study that I have seen reported is the recent one made by four board of health officers in Chicago and reported by Bundesen *et al.* (1940). All the children, comprising a total of 1805, were seen in their own homes and were considered to have been thoroughly exposed because in each instance the physician visited the home only when measles was reported to be present in one of the children and all the homes were of the poorer overcrowded sort in which few children escape the disease. Wherever possible the younger children were inoculated and the older susceptibles (*i.e.*, with no history of having had measles) used as controls, but this was fair since the age distribution of the controls shows that there were plenty of very young children among them: under one year, 14; one to three years, 115; four to nine years, 186; ten years and over, 13. Altogether, 678 received immune globulin, 299 convalescent serum, and 828 were held as unprotected controls. In the globulin group, 52.1 per cent failed to contract the disease and the total of those protected (*i.e.*, no attack or a modified attack only) was 95.2 per cent. In the serum group, 73.2 per cent did not contract the disease and the total proportion protected was 97.9 per cent. In the control group, 26.6 per cent did not contract the disease, but in this group many who came down with it had only a mild attack, so that 'protection' here (in the sense of no attack or a mild attack as used above) was 82.9 per cent. Therefore, one may say that serum was slightly superior to globulin and both were vastly superior to no treatment at all, in the matter of completely preventing the occurrence of the disease, and that from the standpoint of 'protection' as the term is used above there was an advantage of 12 to 15 per cent in using one or the other of the agents. In addition the following facts regarding severity of the disease must be carefully weighed: of those given globulin and later contracting measles, 78.9 per cent were prostrated, of those coming down after serum, 73.7 per cent were prostrated, of those attacked without any protection, 97.4 per cent were prostrated.

Timing the Injections—It is usually stated that if these agents are given from the first to the fourth or fifth day after exposure complete protection is afforded and that if they are given from the fifth or sixth to the ninth day only attenuation of the attack will be accomplished. But since the disease is considered to be contagious as soon as the early catarrhal symptoms appear it is very difficult to know just how long the exposure has been (one very rough rule is that the contact will have been exposed four days when the rash appears on the sick child). In the study of Bundesen *et al.*, above cited

there was very little variation in the results where the injections were given before or shortly after the fifth or sixth days, but in the study of Top and Badger (1941), in Detroit, in which convalescent serum was given to 1183 contacts exposed in homes, there was an appreciable advantage (from the standpoint of avoiding the disease altogether) in giving the injection during the first three days and somewhat less up to and including the sixth day, the most noticeable effect being in the group under one year of age

Dosage—A much used rule with regard to convalescent serum is that stated by Schwartz (1941) give 3 cc to any child up to three years and an additional 1 cc for each year thereafter. The Milwaukee Serum Center starts its recommended dosage at 5 cc, gives 7.5 cc to children over three years, and 10 to 15 cc to adults. Karelitz and Schick, in 1935, found it of advantage to increase their routine dosage to 8 cc, and in his later reports Karelitz has stressed that intensity of exposure has much to do with results. Thalheimer (1939) says that their experience in the Serum Laboratory in New York indicates that in those in whom it is imperatively necessary to prevent measles and also in children in crowded and unhygienic living quarters it is advisable to give one and one half to two times the standard dose. Top and Badger, above cited, gave 10 cc routinely regardless of age but feel their results might have been better had they followed the rule of the London County Council give a dosage in cc which is twice the age, except that minimum dose should be 5 cc. Immune globulin is usually given in dosage of 2 to 4 cc but dosage up to 10 cc has been employed (Laning and Horan, 1935, Hohnson, 1938, etc.)

Convalescent Serum in Therapy—Hyland and Anderson (1937) felt that they modified the attack in 4 patients to whom serum was given after fever and Koplik's spots were present but before the rash had appeared. Kohn *et al.* (1933-1941) felt that the intravenous administration of 40 to 50 cc of the serum is indicated in debilitated children, in those recovering from whooping cough and other infectious diseases, and in children in whom measles developed during the course of another acute or chronic disease. They treated 29 children in the pre-eruptive stage (see Hyland and Anderson, above) and thought that definite modification was obtained in 23 of them. Thalheimer says he receives many reports of the satisfactory use of 10 to 20 cc intramuscularly, but at the time of his report (1939) was still skeptical of the value of this practice.

Adult Whole Blood—Following the results reported by Degkwitz (1920), in Germany, the use of adult whole blood gained wide recognition on the Continent, but in America no great amount of interest in the method was shown until Park urged its more general adoption in 1930. The thing is simplicity itself. About 30 cc of blood (Thalheimer, 1939, says that 40 cc is the minimum amount which should be used) is drawn from a vein at the elbow into a sterile syringe and then half of it is immediately injected into the child's right buttock, the other half into the left. The use of a syringe lubricated with sterile liquid petrolatum and containing 5 cc of a 10 per cent sterile sodium citrate solution will retard clotting, but these precautions are not necessary if quick transfer of the blood from donor to recipient can be made. Blood typing is unnecessary since the injections are made intramuscularly, reactions may occur either immediately or after four to ten days, but they are infrequent and usually not severe. It is probable that in children

above five years of age double the amount of blood should be used, but it is well to remember that the principal object of the procedure is to insure a mild attack rather than to prevent the disease altogether. Unfortunately, parents often look upon these whole blood injections as "cruel" and for some reason consider the procedure rather barbarous, perhaps because the word "serum" has a more scientific connotation for the layman than the familiar and repugnant "blood." The method has gained few steady advocates in the profession. In the experience of Kohn *et al.* (1939) no effect was obtained by injecting whole blood in the pre-eruptive or early eruptive stages.

Fresh Parental Serum—Barenberg *et al.* (1939) have reported upon their very interesting method through use of which they state they have kept their ward free from contagious disease for several years. When a child is admitted, from 60 to 75 cc. of blood is collected from the accompanying parent and stored in the refrigerator, if the Kahn test, received in twelve hours, is negative, 20 to 30 cc. of the serum from this blood is given the child intramuscularly (if the Kahn test is positive, he receives serum from other recently received blood). No discomfort or reactions have been noted.

Immune Globulin (Human)—Observations on the presence of immune bodies in the blood from the umbilical cord have been made by a number of observers and the globulin "extract" obtained from such pooled placental serum has come to be very much used, largely as a result of the efforts of McKhann and his associates (1933-1937). So long as nature continues to take its course there will always be a supply of placentas from which to obtain immune globulin, and therefore this agent is available to all physicians through pharmaceutical houses whereas convalescent serum is only to be had in some of the larger metropolitan centers where there are special laboratories for its collection and preservation. But, as in the case of the sera, we have as yet no means of standardizing the globulin preparation.

Reactions, perhaps due to the inclusion of tissue proteins in the finished product, have caused many physicians to be chary of the use of this placental material. In McKhann's record of 2896 injections, in 36 per cent of the instances there was a local reaction of sufficient degree to be called to the physician's attention, and in 5 per cent this reaction was moderately severe, a febrile reaction occurred in 19 per cent of the patients, and in 3 per cent the temperature rose above 101°F (about 38°C). Since some children had both local and febrile reactions, McKhann considers it "safe to say" that in about 8 per cent of cases there were moderately severe reactions. Injections of immune globulin do not sensitize the patient to subsequent injections, but it seems that a very small number of instances of serum sickness have been recorded.

There are indications that a certain measure of protection, without reactions, may be obtained by administering the agent by mouth in ice water upon an empty stomach, using 2 or 3 times the intramuscular dosage. I have seen no studies of this method since that of McKhann *et al.*, in 1935.

MILIARY FEVER

This is a disease of unknown etiology that occurs in limited epidemics of not more than a week or two. There is high fever, great sweating, profound prostration, and an erythematous rash with miliary vesicles. Between 1718 (when it was first described, though it had probably existed before) and 1861 there were about 175 epidemics recorded in France alone, Italy and southern Germany have also known the disease, but not, I believe, Great Britain. The last reported outbreak occurred in France, in 1926. The mortality is usually low.

It is very doubtful if this disease is the same as that "sweating sickness" which devastated England and the Continent several times in the fifteenth and sixteenth centuries, for John Kaye or Caius, an eminent London physician who described the outbreaks of 1552, had nothing to say about an eruption of any sort.

THERAPY

I do not know of any treatment that warrants particular description.

MUMPS

(*Epidemic Parotitis*)

Mumps is an acute infectious disease probably confined to man, though allegations are sometimes made that it is seen also in goats, dogs and cats. It occurs all over the world and tends to become epidemic during the winter and spring months, but is much less contagious than measles, chickenpox and whooping cough. The greatest age frequency is between five and fifteen years, but the disease also often occurs among young men crowded together, as in barracks or ships or prisons, and among student nurses in hospitals. The Surgeon General of the United States Army reports that in 1918 mumps accounted for 7.15 per cent of admissions to army hospitals, the total number of cases of this disease being 166,370. It was the fourth disease on the list of admissions, both in America and abroad, according to Wollstein, but it was the second largest cause of loss of time. Surgeon General Parran (1940), of the USPHS, has also recently said that mumps is second only to the venereal diseases among the disabling acute infections of recruits. Attacks in early infancy and in the years beyond forty are rare but not unknown. Unusual but well authenticated second, third, and even fourth attacks are on record. A case has been recorded complicating pregnancy in which the symptoms were so severe as to jeopardize the patient's life.

The chief symptom of mumps is a swelling of one of the parotid glands accompanied by stiffness of the jaws and pain which is accentuated upon opening the mouth or attempting to swallow. There is usually a slight rise in temperature. In some cases the opposite parotid swells also but involvement of the other salivary glands is infrequent. Only in the more severe cases do the constitutional symptoms progress beyond slight prodromata.

such as headache, chilliness, and loss of appetite. A slowed pulse rate and lymphocytosis are observable in practically all cases. Greene and Heeren (1937) say that the spleen becomes palpable in many cases. The attack is usually terminated within a week of its inception. A quarantine period of two or even three weeks is often enforced, but since experience indicates that communicability very rarely extends beyond the duration of the swelling, Gordon and Heeren (1940) consider the following regulations satisfactory: (a) Keep children exposed at home away from school for three days to see whether they too are affected. (b) Take them out of school again from the fourteenth through the eighteenth day to cover the period of incubation in them should they have become infected. (c) Isolate the sick child until the swelling of the gland has subsided, or at least seven days. Orchitis occurs in about 18 per cent of boys past puberty and young men who are attacked by mumps. It is frequently preceded by epididymitis, is accompanied by fever and a considerable degree of prostration, and results in atrophy of the testis in about half the cases. It does not seem that anyone has followed a series of orchitis cases to determine how many of these individuals become sterile but the occurrence is believed to be rare. Loss of secondary sexual characteristics, libido, or the ability to perform the sexual act is extremely rare. The exact incidence of oophoritis is unknown though it is doubtful if this complication is really less common than the corresponding one in the male. Both primary orchitis without parotitis and primary oophoritis have been reported occasionally. Other complications are also rare and mild, except that in some epidemics a benign type of encephalomeningitis occurs in some of the cases, both Finkelstein (1938) and Fox (1941), the latter of Milwaukee, believe that this complication is of more frequent occurrence than generally believed. Deafness, unassociated with meningeal involvement, occasionally occurs and is usually permanent, there are other varied and striking nervous complications but they are not often seen.

Wollstein was, I believe, the first to show that the virus of mumps (first conclusively demonstrated by Johnson and Goodpasture, in 1935) is present in the mouth secretions of individuals having the disease. Droplet infection is therefore probably the rule, since transmission can take place before the swelling appears, we do not as yet know whether there are many, or any individuals who are carriers of the disease. Eighteen days is considered to be the usual period of incubation.

THERAPY

Very little treatment is indicated save for relief of pain by the prolonged use of hot or cold applications or of U.S.P. belladonna ointment applied over the swelling. The attempt is sometimes made to have an antiseptic mouth wash used to prevent secondary infection, but this measure, if properly employed, adds greatly to the pain in most cases and is of very doubtful value. However, when the mouth must be kept artificially moistened when the salivary ducts have become occluded by swelling, there is no reason why the fluid used should not be some such antiseptic as diluted Dobell's solution.

It is generally believed that the incidence of orchitis will be greatly lessened if absolute bed rest is enjoined in boys and young men, but there are observers who doubt the possibility of statistically proving the point. The

usual practice when the complication develops is to support the inflamed scrotum and make use of cold applications in a fluffy light manner so as not to increase the discomfort by their weight. A local application of 50 per cent methyl salicylate in hydrous wool fat (lanolin) is said to be serviceable. Wesselhoeft informs me that in severe cases he still very successfully employs the treatment which he advocated a number of years ago: incision through the tunica vaginalis and multiple incisions of the tunica albuginea to bring about relief of pain through permitting escape of the serous fluid imprisoned under pressure. The operation takes about one minute under gas.

It is doubtful if the use of convalescent serum after the attack of mumps has developed alters the course of the parotitis but it is alleged to lessen the incidence of orchitis and hasten its subsidence if already established. In the reports of Teissier and of Lavergne and Florentin some years ago it was found that doses of 40 cc are the most effective given intravenously. Thalheimer (1939) says they have a number of recorded instances at the Serum Center in New York in which such therapy seemed helpful but feels more experience is needed before true evaluation can be reached. Gordon and Heeren's (1940) present attitude is one of skepticism.

PROPHYLAXIS

Regan in 1925, if not the first was certainly one of the earliest users of convalescent serum intramuscularly in attempted prevention of mumps. Since that time there have been numerous reports and practically all of them favorable but studies of series in which there were adequate controls are conspicuously missing. The reason for this is of course the fact that the serum is usually employed only when it seems imperatively necessary to prevent spread of an epidemic, as in boys' camps, wards filled with debilitated children, etc. A typical recent report is that of Kutscher (1940) who injected 51 susceptible boys between nine and sixteen years of age all thoroughly exposed to a case that had developed in camp giving 8 cc to the younger and lighter and 10 cc to the older and heavier boys (Thalheimer recommends 20 cc for children and 40 cc for large adolescents and adults), 1 case developed ten days after the first but thereafter no other case during the remaining five weeks of the camping period. Lyday's (1941) experience indicates that 10 cc of serum confers a passive immunity of probably only very short duration and that perhaps it would always be well to reinject upon subsequent exposures even if they follow the first exposure by only a few days.

Gordon and Heeren (1940) say that for preparation of convalescent serum blood is preferably collected two to three weeks after the attack but that it is satisfactory in emergency to take it from persons who had their attacks many months before.

MYCOSES

ACTINOMYCOSIS

Actinomyces is a chronic infectious disease caused by the ray fungus (*Actinomyces bovis* being the type species), which probably exists normally among the abundant flora of the alimentary tract and gains access to the tissues through microscopic lesions, carious teeth wounds made by penetrating foreign bodies, or reaches the respiratory tract by aspiration from the mouth and pharynx. The disease occurs quite commonly in cattle ('lumpy jaw'), but there is no good evidence that it can be conveyed from cattle to man, or indeed from man to man. Though looked upon as a rare disease, recent statistical studies tend to show that it occurs with much greater frequency than has heretofore been believed. Most of the cases in the United States have been seen in the upper Mississippi valley and the northwestern states, country folk are much more often affected than city dwellers.

The essential lesions of the disease are multiple, more or less painless abscesses, usually surrounded by a considerable area of proliferative tissue. Discharging sinuses develop from the abscesses, and the process extends by continuity of tissue or sometimes by metastasis. Fifty per cent of reported cases have been in the region of the head and neck, usually beginning about the jaw, and here the diagnosis is not difficult. In about 20 per cent of cases some abdominal organ is primarily affected, here the diagnosis is more difficult until the lumpy process extends to the abdominal wall and a characteristic sinus appears. In approximately 15 per cent of cases the involvement is thoracic with physical signs usually indistinguishable from pulmonary tuberculosis until perforation of the external wall takes place. Rarer forms of the disease may occur anywhere in the body.

Under proper treatment the prognosis may be considered fair in the head and neck cases, very bad in pulmonary and perhaps slightly better in abdominal cases.

THERAPY

Iodides—Sodium or potassium iodide used to be considered specific in a limited way in actinomycosis, but nowadays much doubt is felt of their real effectiveness. Certainly their use in large doses must be persisted in for a long period of time—so long indeed in many instances that one must wonder whether it was really the iodides that finally produced whatever amelioration was obtained. Unfortunately, most patients tolerate the drug well. I recall a case in which I gave 640 grains (42.6 Gm) of sodium iodide daily for a period of many months, 60 grains (4 Gm) intravenously and the remainder by mouth. During this time the patient was delivered of a normal baby and neither the mother nor the child showed any signs of iodism. Dosage even much higher than this has been employed not infrequently.

Thymol—Myers (1937) reported good results with thymol administered in capsules of 22 to 30 grains (1.5 to 2 Gm) daily or on alternate days, in some instances the drug was also injected into the sinus tracts in a strength of 10 to 20 per cent in olive oil. Myers' cases were of the localized type not involving internal organs. In a small series of similar cases Joyce (1938) also had very good success with thymol combining its use, however, in

most instances with the employment of surgery. In Clemens' (1940) case apparent recovery occurred under the drug after both a sulfonamide and deep x ray therapy had proved ineffective. The thymol is usually given in a single dose in milk before breakfast. Clemens' patient tolerated twenty eight days of this medication without gastro-intestinal or other disturbance. Etter and Schumacher (1939) report the progressive improvement and apparently complete recovery of a patient with primary pulmonary actinomyosis under thymol.

Sulfonamides—There have been a number of reports usually of only a single or a few cases, of the successful use of these drugs when other agents had failed. The most recent report I have seen is that of Dobson *et al* (1941) in whose three cases—one with involvement of the jaw, one of the chest and one of the abdomen—complete cure was apparently obtained with sulfanilamide (see dosage in Sepsis). However, Minton (1940) failed in his 2 cases and Clemens (see above) succeeded in his case with thymol after a sulfonamide had failed.

Surgery—It is now the consensus that surgery should be boldly and persistently employed wherever the involved tissues can be radically curetted or widely excised. Wangensteen (1938) says that having set out a few years ago at the University of Minnesota to make a comparative study of iodides, surgery and irradiation he obtained such satisfactory results with surgery that he never got around to trying the other measures. He says he has learned that mere curettement and keeping the wound open by packing is just as effectual as excision. Cutler and Gross (1940) feel that the advances made in thoracic surgery in recent years now justify very bold attempts to save life in apparently doomed pulmonary cases.

X-ray—Roentgenologists are beginning to think very well of their results not only in the apparent but in the deep-seated lesions also. Auster (1940), in a recent review of the entire subject of actinomyosis expresses the opinion that x ray will undoubtedly play a more important part in the handling of this entity as time goes on. Cutler and Gross feel that the relative innocuousness of the procedure often makes trial of x ray worthwhile.

Miscellaneous Measures—None of the following have consistent successes to recommend them: colloidal gold, colloidal copper, copper sulfate, non specific protein therapy, autogenous vaccines.

BLASTOMYCOSIS AND PULMONARY MONILIASIS

Blastomycosis is an infectious but apparently noncontagious disease caused by a number of closely allied species of fungi, which may be called here the *Blastomycetes*. The impression that most cases in the United States have been reported from the vicinity of Chicago and from the state of Louisiana seems to be false, for though many cases have been seen in both Illinois and Louisiana, there is a wide scattering of reports throughout the country. The disease is known elsewhere in both hemispheres, but Moore (1938) divides blastomycosis into three types, North American, European, and South American. The subject, as recently shown by Smith (1941), is becoming very complex.

Blastomycosis, as we know it in this country, affects usually the skin only but deep-seated involvement of the lung bones and of any of the internal

organs, but especially of the lungs, occurs not infrequently. The cutaneous lesions take the form of papules, pustules, nodes, abscesses, or ulcers, and this form of the disease runs a course of many years during which active and quiescent periods alternate, when there is involvement of internal organs the prognosis is very bad. In the pulmonary cases the presenting symptoms are usually not easily distinguishable from those of tuberculosis. Some of these bronchial and lung involvements are not strictly blastomycotic in origin but are due to yeasts of the genus *Monilia*, they are therefore separately designated "pulmonary moniliasis."

THERAPY

Iodides are used in large dosage here as in actinomycosis. Martin and Smith (1939) warn, however, that they may occasionally do harm in a patient who has become allergic to the infecting fungus. They therefore routinely skin test their patient with *Blastomyces* vaccine and if he is hypersensitive they desensitize him with gradually increasing doses of vaccine before beginning the use of iodides. Bush (1941) felt that the improvement in his case was due to supplementing large oral dosage of iodides by the daily intravenous administration of 15 minims (1 cc), later increased to 30 minims (2 cc), of compound solution of iodine (Lugol's solution) plus 15 grains (1 Gm) of sodium thio sulfate, x ray therapy was simultaneously employed in this case. Most skin cases yield to iodide therapy if it is begun before there is involvement of the deeper structures and if it is persisted in sufficiently long. In those rare cases where it is possible, total excision of the affected part is possibly the ideal treatment, but according to some observers it must be excision and not merely curettage, for this latter procedure is thought to have been responsible at times for a spread of the disease. Copper sulfate has been used effectively in some cases in doses of $\frac{1}{4}$ to 1 grain (0.015 to 0.06 Gm) three times daily by mouth. Recently, x ray therapy and diathermy seem to have proved themselves definitely useful, as cited above in Bush's case. Hedge has reported (1928) 2 cases in which complete cure without any sign of recurrence in more than a year was accomplished by the application to the lesions of carbon dioxide snow under moderate pressure for ten to fifteen seconds. Pupo's (1929) 4 cases were successfully treated with intravenous injections of 10 cc of 1 per cent methylene blue, or alternated with injections of 5 cc of 0.5 per cent trypanavin (acriflavin), according to the seriousness and obstinacy of the case.

In the disseminated form involving the internal organs all therapy seems to be hopeless, Decker's (1939) recent success with iodides in a pulmonary case being probably the exception to prove the rule. In the case of Solway *et al* (1939) large doses of a sulfonamide were used without any obvious effect. Steinfield (1931) recommended yeast vaccines in pulmonary cases, and Bakst *et al* (1934) used an autogenous monilia vaccine with satisfaction in a single instance. Flinn *et al* (1935) thought that the substitution of milk sugar for all commercial sugars was probably helpful in one of their monilia cases.

CHROMOBLASTOMYCOSIS

This is a fungous disease of worldwide distribution but of rare occurrence. Emmons *et al* (1941) have just reported the sixth case in the continental United States but they consider it likely that numerous other cases have

hitherto goes unrecognized. This mycotic infection with *Hormodendrum pedrosoi* or several related organisms such as *Phialophora verrucosa* in the causative role has been much studied by Carrion and his associates in Puerto Rico and Moore and his group in Argentina. Pardo Castello *et al* (1912) confirming Weidman's earlier statement that this disease was being encountered in Havana also have recently reported 31 cases observed in Cuba. Classically the disease which is often associated by the patient with injury by wood or vegetation presents as a slowly progressing group of pink or violaceous verrucous or papillomatous lesions usually on the legs or feet; there are often cauliflower like excrescences which readily ulcerate. But many of the cases have differed widely from this description so that apparently clinical recognition of the entity without laboratory aid is not easy. Some dermatologists feel that perhaps some cases now being diagnosed histomycosis are in reality chromoblastomycosis.

THERAPY

It seems that these cases usually respond well to iodides but these classical agents were worthless in Pardo Castello's experience. He prefers intensive roentgen therapy for the superficial types and electrocoagulation for the more extensive and infiltrated conditions.

SPOROTRICHOSIS

Sporotrichosis is an infectious disease caused by a fungus of the genus *Sporotrichum*. Most patients have been farmers or those otherwise in intimate contact with shrubs or the soil. Cases have been reported all over the world but the disease is apparently most frequently recognized in France and in the upper Mississippi valley in the United States.

Sporotrichosis is characterized by the appearance of a subcutaneous nodule which attaches to the skin, breaks down in the center, and becomes chronic as a cold abscess whose periphery remains well defined and indurated. A number of these lesions may appear on widely scattered portions of the body but it is more usual for an ascending lymphangitis to develop from the primary nodule (the chancre) with numerous lesions appearing along its course. Montgomery and Holman (1935) emphasize the fact that pseudo-epitheliomatous changes may cause malignancy to be suspected in some of these cases. The disease is usually chronic and in the United States the inflammation is of so low an order that there is little pain and practically no disturbance in the general health but in France it would seem that radical amputations are often necessary and that visceral involvement is frequent (possibly their cases are not all truly the entity we recognize here as sporotrichosis?).

THERAPY

Here again the iodides in large doses are usually curative. Their use must be persisted in for a considerable time after apparent cure to prevent recurrence. Wade and Matthews (1935) successfully treated a patient through pregnancy and delivery and without any effect upon the infant. Such tempting surgical procedures as radical incision or curettage should be avoided as they only prolong the process. However abscesses which show no tendency

to resorption are sometimes aspirated with advantage, it is the practice usually to refill the cavity with a weak iodide solution (1 per cent). It is said that x ray treatment sometimes hastens the disappearance of the lesions but this is looked upon by most men as merely adjunctive therapy.

STREPTOTHRIX

This is a very rare disease caused by a fungus like organism called, perhaps erroneously, *Streptothrix*. In the small number of cases reported the lungs have been principally involved, though in a few there was implication of other organs as well. The symptoms are those of pulmonary tuberculosis, abscess and bronchopneumonia—a confusing picture. I believe that all proved cases of streptothrix infection have terminated fatally.

THERAPY

I know of nothing to describe.

COCCIDIOIDOMYCOSIS

(*Coccidioidal Granuloma and Paracoccidioidal Granuloma (Almeida's Disease)*)

This disease is caused (in North America at least) by the fungus, *Coccidioides immitis*. Practically all of the cases seem to have been contracted in the San Joaquin Valley in California. Kessel (1941) has just brought the total number of cases seen in California up to 660. However, students of the disease believe that this geographic distribution is more apparent than real for they feel that in other parts of the country some patients similarly affected die under a false diagnosis, indeed, Farness (1941) has reported 5 cases apparently contracted in Arizona. A large number of cases of a similar disease of somewhat milder form have been reported from South America, where it seems to be caused by the radically different fungus *Paracoccidioides brasiliensis*, Jordan and Weidman (1936) proposed for this latter disease the designation "paracoccidioidal granuloma (Almeida's disease)." The symptoms of the North American type very closely resemble those of blastomycosis with, in addition, the appearances of a fulminating pulmonary tuberculosis, but almost any other disease may be simulated and there also occurs a chronic form extending over several years. Prognosis is very bad. Dickson's studies, begun in 1937, indicated that "valley fever" of the San Joaquin Valley (bronchopneumonia, high fever, painful erythema nodosum, recovery either very prompt or within a few weeks) may be the primary acute manifestation of the coccidioidal infection, I believe that this is now generally accepted to be true. Smith (1949) has reported 492 diagnosed cases of this "valley fever" that had occurred in a period of seventeen months and this is taken to indicate that probably many thousands of individuals are actually attacked. It is assumed that the most common portal of entry for the fungus is through the lungs by inhalation and next through the abraded skin. The incubation period is thought to be one to three weeks but I believe no exact knowledge exists on the point. Kessel probably expresses the opinion of many when he says that the coccidioidin skin test is only of relative and not absolute value.

THERAPY

The best hope such as it is for these unfortunates lies in early and radical amputations where possible. Among the medicinal and other agents each of the following has one or two successes to its credit and many more failures (a) Iodides, (b) intravenous dyes, (c) colloidal copper, the 5-cc ampule intramuscularly at four-day intervals, (d) autogenous vaccines and foreign protein shock therapy (Jacobson, 1939, has described some successes with a vaccine he prepares in Los Angeles), (e) thymol by mouth, beginning with 15 grains (1 Gm) daily and working up to four times that amount until a total of 104 Gm has been given in twenty four days, administered (50 per cent) in olive oil in capsules during meals, 33 per cent used for irrigation also (Sox and Dickson, 1936), (f) tartar emetic and x rays the antimony potassium tartrate from 2 to 8 cc of a 1 per cent solution intravenously on alternate days, one half skin unit of unfiltered roentgen rays at ten to fourteen day intervals (Tomlinson and Bancroft, 1934).

Farness (1941) says that the sulfonamides have not as yet shown themselves to be the agents of choice.

MADUROMYCOSIS

(*Madura Foot, Mycetoma*)

Maduromycosis is a chronic affection of the foot occasionally the hand and much more rarely other portions of the body such as the knee or thigh or even one of the internal organs, caused by fungi of a number of different genera and species. It has been known since time out of mind in India, where it was first scientifically described and is reported rather frequently from many other tropical countries. However, its occurrence is by no means confined to these warm regions for it has been recorded all over the world. Hanan and Zurett (1938) say that 43 cases have been reported in North America.

The disease usually follows a penetrating wound, most frequently in a barefooted person and practically always in a rural area. Following its implantation in this way the fungus grows within the deep tissues and causes necrosis which eventually reaches the surface. The typical lesion is a deep sinus that is discharging a foul smelling oily fluid containing certain characteristic grains. The whole foot may be riddled with a network of intercommunicating sinuses of this sort and is much swollen and characteristically deformed. Pain is usually of a dull aching sort and constitutional symptoms are slight and inconstant. The disease may last many years, there is no tendency to heal.

THERAPY

Internal medication is a failure. Local measures are of no avail. Amputation is the only treatment of value. I think I should add, however, that Dixon (1941) has successfully used sulfanilamide internally in a case which had the physical characteristics and clinical course of maduromycosis, though the attempt to culture the organism was unsuccessful.

TORULOSIS

It is only in recent years that distinction has been drawn between cases of torulosis, coccidiosis and systemic blastomycosis. With the recent single case reports of Binford (1941), and of Stiles and Curtiss (1941), and the six cases of Reeves *et al* (1941), the total number of reported cases of torulosis is brought up to 81, but it is considered likely that many times this number of cases have gone unrecognized. Freeman exhaustively reviewed the subject in 1931. In most of the recorded cases infection has involved primarily the brain and cord with symptoms closely simulating tuberculous meningitis or brain tumor, with this difference that *Torula histolytica* (Mook and Moore say that *Cryptococcus* is the correct generic name) is usually abundantly present in the spinal fluid. In a few cases there have been cutaneous, joint, Hodgkin's like, pulmonary and other visceral involvements, Robertson *et al* (1939) very pertinently point out that an entity which can simulate a great many other maladies is worthy of more than passing interest to any practitioner. Longmire and Goodwin (1939) have reported the sixth case of generalized involvement, including in their case the brain, meninges, lungs, liver, spleen, kidneys, pancreas, thyroid and aorta.

THERAPY

All the measures used in other mycotic infections are tried here but it is not a matter of record that any of them has been of the least avail. Pathogenicity seems to be relatively low until the central nervous system is involved and then the prognosis becomes immediately and absolutely bad, a few cases are recorded however, in which self arrest has seemed to occur for a short time at least.

HISTOPLASMOSIS

(*Reticulo endothelial Cytomycosis*)

In 1905, Darling found 3 cases in the Canal Zone which presented a clinical picture somewhat similar to visceral kala azar but from which he obtained the organism *Histoplasma capsulatum*, since determined to be a fungus. The entity, to which in the course of time the title 'histoplasmosis' has come to be applied, is a very complex and puzzling one and hence the number of reported cases has risen very slowly. Meleney, thoroughly and authoritatively reviewing the subject in 1940, brought the total of cases up to 32, but since that time Brown *et al* (1941) at the Mayo Clinic, Rhodes *et al* (1941) in Cincinnati, Reid *et al* (1942) in Richmond, and Hild (1942) in Houston have each reported a single case, and Anderson *et al* (1941) have added 2 cases from St. Louis. The first identification of the disease before death was accomplished by Dodd and Tompkins in 1934. Also in 1934, De Monbreun cultured the organism, though actually in 1933 Hansmann and Schenken had reported a case from which they cultured an organism which they classified in the genus *Sepedonium* though stating that it resembled Darling's organism—many mycologists now consider that these workers were also dealing with *H. capsulatum*. The organism is transmissible to numerous laboratory animals and has been recovered from a naturally acquired case of the disease in a dog by De Monbreun (1939), who makes the interesting suggestion that perhaps in histoplasmosis there is still unrecognized a common

and milder form of the disease in man comparable to "valley fever" in coccidioidomycosis

According to Meleney the clinical picture may resemble that of kala-azar, Hodgkin's disease, leukemia, lymphosarcoma, aplastic anemia, or pulmonary or miliary tuberculosis, or it may begin as a small skin lesion which develops into a generalized ulcerative skin condition. Since the organism may be demonstrated with proper technique in the blood and in the tissue cells, obviously the diagnosis rests upon having this "new" disease in mind in a puzzling case which does not easily fall into one of the other categories.

THERAPY

Few cases have been recognized while there might still have been chance for effective therapy, so there is little treatment to describe. The iodides and arsphenamines seem to have been of little value. Meleney (1940) believes that antimony deserves especial trial, either as antimony sodium tartrate (tartar emetic), or as pentavalent compounds as used in kala-azar, or trivalent compounds as used in hileriasis. Both Rhodes *et al* (1941) and Anderson *et al* (1941) have failed to halt the progress of the disease with sulfonamides.

OROYA FEVER AND VERRUGA PERUANA

(Carrion's Disease)

Carrion's disease has until very recently been thought to be peculiar to certain cleft valleys on the western slopes of the Peruvian Andes, where it manifests itself in two forms: one, Oroya fever, a constitutional and fatal malady, and the other, verruga peruana, a cutaneous and nonfatal affection. It has been endemic in this region since early historic times. Many of Pizarro's invading troops were at one time thought to have perished of this disease but now it is not certain that they did so, in more recent times it has taken a heavy toll in all the heroic railway building ventures that have taken place in these cruel mountains. The latest recorded outbreak of the disease occurred in southern Colombia, an epidemic in which there were 1800 deaths in about 4000 cases. The first Harvard Commission, formed to study the matter in 1913, cast considerable doubt upon the common causative factor in the two conditions, but this was dispelled by the work of Noguchi, Battistini and Herceles, in 1920, who cultured *Bartonella bacilliformis* from the blood of an Oroya fever patient and produced Oroya fever or verruga peruana in monkeys by inoculating them with this culture, the particular manifestation produced being entirely dependent upon whether the intravenous or the intradermal method was used. They also produced Oroya fever by inoculation of material taken from a verruga nodule and obtained a pure culture of the organism from the blood of the inoculated animal.

It is considered extremely likely that some blood sucking insect is the transmitter of the disease but the sandfly is not yet completely convicted.

in Peru In the affected region in Colombia the sandflea is said not to occur and I have seen the statement (but not the actual record of the observation) that it has been transmitted there to guinea pigs by lice from a human patient According to Fox (1935), it is the consensus in Peru that many animals suffer spontaneously from the verrugous type of the malady, certain plants seem also to serve as a reservoir for the causative organism and as food for the insect vector Weinman and Pinkerton (1937), of the second Harvard Commission, found healthy human carriers of the disease in an endemic region in Peru One thing is certain, that if the stranger leaves the endemic valley before nightfall his liability to contract the disease is much lessened The incubation period is from two to three or more weeks, it was twenty-one days in the experimental infection of the young student, Carrion, who died a martyr to his investigations

Oroya Fever—This type of the disease is characterized by a rather abrupt onset with weakness, malaise, slight rigors moderate irregular fever, and a rapid pernicious anemia with the parasites present in the red blood corpuscles The mortality is variously estimated at from 40 to 80 per cent, but as many of these patients are affected with other chronic tropical diseases at the same time it is perhaps unfair to ascribe all the deaths to uncomplicated Oroya fever The study of Ribeyro (1932) indicates indeed that the prognosis is favorable in simple uncomplicated Oroya fever and that the only complication which makes death almost certain is due to paratyphoid B bacillus The fatal cases run their course in a few weeks

Verruga Peruana—This type is characterized in the beginning by joint pains and a moderate fever of short duration after which the eruption appears This eruption is at first milary and is usually confined to the arms and legs, but it may occur elsewhere on the body and even on the mucous membranes In most cases the rash becomes papular and subcutaneous nodules appear Some of these nodules, attaching to the skin and ulcerating are called "verrugas" and have given the disease its name The mortality is also high in this type, but individuals who are not harboring other malicious tropical diseases at the same time nearly always recover Only the ulcerated lesions leave any scars Fox (1935) has described the dermatologic lesions in detail

THErapy

Despite the havoc which Carrion's disease has wrought and the interest it has aroused in the modern scientific mind, no effective treatment has been devised unless it prove to be the new arsenic antimony compound, Sdt 386 B of Kikuth (1937), with which he says Manrique has successfully treated 14 cases Strong (1940) says it is the consensus among conservative physicians in Peru that the drug is not of value Patino Carmargo (1939), discussing the Colombian outbreak, says that vitamins, calcium, antimony and arsenic gave excellent results, but he gives no details regarding the use of these agents In view of Ribeyro's report (see above) the imperative necessity for protective vaccination against typhoid paratyphoid organisms of all persons who are obliged to visit Oroya-infested regions, is quite evident

PAPPATACI FEVER

(Three day Fever, Sandfly Fever)

This disease, which is caused by a filtrable virus conveyed by the bite of night biting sandflies of the genus *Phlebotomus*, is common in tropical and subtropical regions wherever this insect occurs. Natives are usually "salted," i.e. relatively immune, but a large proportion of newcomers to an infested region contract the disease. In World War I it interfered seriously with operations in the Mediterranean basin and the report of Walker (1940) dealing with the operations then current in Palestine, indicated that it was seriously if only temporarily incapacitated troops again in the current war. Sandfly fever is usually characterized by abrupt onset with a fairly high fever, severe joint and muscle pains, headache, malaise, and a characteristic flush of the face and neck. The fever usually drops by crisis on the third day and the other symptoms abate, but the flush persists for ten to fifteen days in about half of the cases. Convalescence is oftentimes slow but all cases recover. Walker says he has seen undoubted second attacks but I understand from his paper that they are of relatively infrequent occurrence.

THERAPY

There is nothing to describe except to say that analgesics such as phenacetin (acetphenetidin), acetanilid and aspirin (acetylsalicylic acid) may be freely used during the time the patient is in bed and feeling very miserable. Walker found the use of an opiate at night occasionally advisable, but Manson Bahr (1940) speaks of opium as the most valuable drug in treatment. The latter also says that lumbar puncture has relieved the headache—surely this radical measure is not often resorted to. The results of Shortt *et al* (1940) with preventive vaccines in India were inconclusive.

PLAGUE

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever. Since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

PNEUMONIA

While recognizing that the differentiation between lobar and bronchopneumonia is not always easy, indeed sometimes impossible, to make at the bedside, I am describing the disease below in these two classical forms because both presentation and understanding are thus facilitated.

Lobar Pneumonia—Lobar pneumonia is one of the most widespread and

dangerous of all the infectious diseases of the temperate zones. Its occurrence in the tropics is relatively rare save in certain restricted areas where extreme undernutrition makes the native population especially susceptible. In about 90 per cent of instances it is caused by *Diplococcus pneumoniae*, in the remaining cases by streptococci, staphylococci, Pfeiffer's bacillus (*Haemophilus influenzae*, which incidentally does not cause influenza), very rarely Friedlander's bacillus (*Klebsiella friedlanderi*) is responsible, but in these instances the physical findings are not entirely typical of the lobar form of the disease. Of *Diplococcus pneumoniae* 32 types are now recognized. During ordinary (i.e., nonpandemic) times, Reimann (1935) found the most ordinarily encountered types to be I, II, III, VIII, VII and V, in approximately that order, while Bullock and Gleich (1938), studying 3817 cases at Harlem Hospital over a period of seven years, found the order to be, I, III, II, V, VIII, VII and IV in adults, among infants and children, XIV and VI also occurred frequently. The old belief has been that pneumonia is auto-infectious; that is, that when resistance becomes lowered the organisms always harbored in the mouth are able to establish themselves on a pathogenic basis in the lungs. Recent studies, however, have shown that the type of organism present in the mouth of most individuals is not the one responsible for most cases of the disease, present knowledge therefore inclines toward the position that pneumonia is contracted by actual droplet infection from an active case or from a recovered case still harboring the causative organism, or from an individual who has become a temporary carrier following such contact, and that the number of chronic carriers is small. But the details of these matters are by no means determined as yet, only one group so far as I am aware (Benjamin *et al.*, 1939) has as yet advocated that pneumonia be treated, and inferentially quarantined, as a contagious disease by public health officials. Recent head cold or gripe, exposure to wet and cold, and excessive fatigue are frequent precursors of the disease, the incidence is decidedly higher among blacks than whites. The average mortality before the advent of effective chemotherapy was: private practice, 15 (1) to 25 per cent, good general hospitals, 25 to 35 per cent, public institutions treating the lowest classes, including many alcoholics, 50 to 60 per cent. But these were the statistics from metropolitan areas, country practitioners always maintained that their mortality was much lower than in the cities, and very probably it was. In general the mortality trend has been downward throughout the world during a long period of years much antedating specific therapy.

Lobar pneumonia is often but not invariably characterized by the suddenness of its onset, typically with a chill, stabbing pain in the side, high rise of temperature and pulse rate, rapid respiration often with dyspnea, cough and rusty sputum, and involvement of the nervous system ranging from mere anxiety to active delirium. Herpes simplex, jaundice (possibly of more frequent occurrence in Negroes than in whites), and initial vomiting are often seen. There are typical physical "findings" in the chest, whose description has no place here. Cyanosis, varying in degree with the respiratory and circulatory involvement, always makes its appearance later. In the average case, if not treated by the newer specific methods the symptoms last for from five to ten days with very little remission and then the attack terminates by a gradual lessening in severity of all symptoms or, in less than half the cases, by a 'crisis' in which the desquamation occurs within twenty-four hours.

Bronchopneumonia—Bronchopneumonia is a diffuse lobular inflammation of the lungs in which several organisms can be identified as the causative factor. There are several types.

(1) **Primary bronchopneumonia**, occurring in children under four years of age. This type is not directly associated with any other disease, is usually mild, and is nearly always caused by pneumococcus, the symptoms are much like those of lobar pneumonia except for the difference in the distribution of the pulmonary lesions.

(2) **Secondary bronchopneumonia** is caused by staphylococcus, streptococcus, Pfeiffer's bacillus (*Haemophilus influenzae*), sometimes Friedländer's bacillus (*Klebsiella friedlanderi*) and rarely the pneumococcus. It is the most dreaded complication of the infectious diseases in children and of the infectious and chronic debilitating diseases of middle and old age, many postoperative pneumonias and some post-traumatic pneumonias are of this type. The symptomatology of bronchopneumonia is too diverse and complicated to warrant description here, suffice it to say that the occurrence of this complication is usually marked by a change in the severity and finally the type of the symptoms which the patient is manifesting, until ultimately the respiratory and circulatory embarrassment, cyanosis, general toxemia and diffuse chest involvement of bronchopneumonia completely overshadow or supersede the original picture.

(3) **Primary epidemic bronchopneumonia**. The mortality is very great in these cases, as witness the epidemic during the first World War. Most of the postinfluenzal pneumonias of that dark period were caused by *Streptococcus haemolyticus*, with or without the accompaniment of other organisms whose virulence had been temporarily raised to a high pitch.

(4) A type variously designated atypical pneumonia, subacute pneumonia, primary virus pneumonitis, and acute interstitial pneumonia. This is an entity, apparently caused by a virus, which is just beginning to be described (the paper of Adams, 1941, will lend the interested reader into the literature).

(5) **Lipoid pneumonia**, in which the congestive, inflammatory or necrotic changes are the result of the aspiration of milk fat, fish oil or liquid petrolatum in recumbent babies or debilitated adults or in healthy individuals who use medicated liquid petrolatum drops or sprays intranasally over a long period of time (see Cannon's [1940] review for the literature). Differential diagnosis of this type of pneumonia in its acute form is rarely made ante-mortem.

In the aged, pneumonia is many times not clear cut in type, the onset may be insidious and the course, which is sometimes even feverless, may be very protracted, high incidence of pre-existing circulatory and renal disease of course much increases the gravity of the situation.

THERAPY

The treatment of lobar and bronchopneumonia can be described together with such exceptions as will be noted later. I shall employ the following subdivision of the subject for convenience: sulfonamides, serum in selected cases, new quinine substitutes, oxygen therapy, nursing measures, dietetics, fluid and chloride administration, symptomatic treatment.

SULFONAMIDES

The history of these drugs in pneumonia has merely been a repetition of the history of all truly specific agents to wit there was never any doubt of their efficacy after the first early trials, reports of their consistently successful use quickly poured in from all over the world and the standardization of methods for their employment with the highest degree of safety and certainty has lagged far behind the universality of that employment

Routine Employment Warranted—It has come to be practically universal custom to begin the administration of a sulfonamide in every case without exception in which the clinical diagnosis of pneumonia has been made This practice has the support and approval of such men of experience as the following (confining ourselves to a few only in the United States) Cecil (1940), Cornell University Hospital, Long (1940) Johns Hopkins Hospital Finland (1940), Boston City Hospital Plummer (1941) Bellevue Hospital In addition one should add that there is full approval of this routine use of the drugs in the recent letter on chemotherapeutic methods published in the Journal of the American Medical Association (Feb 8 1941) for the committees composed of leaders in this field, who studied the matter as applying to military personnel for the National Research Council

Effect upon Mortality Rate—Plummer (1940) gathering 966 cases from the literature found a mortality rate of 8.5 per cent as compared with 32.8 per cent in a much larger series treated without chemotherapy and earlier analyzed by Hefron In 129 bacteremic cases there was a mortality of 26.7 per cent as against Hefron's calculated figure of 61.8 per cent Flippin *et al* (1941), at the Philadelphia General Hospital have had a mortality of 9.8 per cent in 386 cases, they excluded patients who had died before receiving adequate quantities of the drug Gaisford (1939), in England, offers a very striking comparison in cases of frank lobar pneumonia in 1936, his mortality was 22.4 per cent in 415 cases, in 1937, 21.7 per cent in 461 cases, in 1938 (using sulfonamide) it was 9.5 per cent in 490 cases—the latter figure included any patient who had had 3 doses even though admitted in *extremis* A further breakdown of his figures is interesting for the mortality under fifty years is seen to have fallen from 16.5 per cent to 1.6 per cent, and over fifty (none over seventy years were included) from 51 per cent to 24.4 per cent Kaufman (1940) has found that even among the very aged in institutions the sulfonamides are surprisingly effective, in his series of 81 cases he had a fatal outcome in only 23.5 per cent though the expected incidence without the drug would have been 75 per cent It seems to me that the truest indication of what can be accomplished under specially favorable circumstances is contained in Ordman's (1939) report the case fatality rate from lobar pneumonia among about 300,000 native laborers in the Witwatersrand goldfields (mostly young individuals and under constant medical supervision) had been between 11 and 13 per cent for the five years preceding the introduction of the drug, under the sulfonamide the rate declined to 2.75 per cent Finland (1940) felt that in the United States we might be able to cut our pneumonia mortality to one fourth or even less and present indications are that we are doing just that, he makes the point that the deaths still occurring are mainly in the very aged, in persons with complicating severe systemic disease, and in those in whom treatment is delayed until they are in a moribund state or focal infections have already become established

Effect upon the Patient—The temperature turns sharply downward after the patient comes under the influence of the drug often reaching normal within or before twenty four hours and practically always under forty-eight hours indeed if fever continues beyond forty-eight hours it is usually found that there is some serious complication or the pneumonia is of a rare type which is resistant to the drug. The respiratory and pulse rates and the leukocyte count also decline and the patient ceases to give the impression of one critically ill, but nevertheless he does not often show that striking change characteristic of normal unaided crisis (the physical signs may persist or even continue to develop for a time). Often there are added to his general 'toxic' feeling the disagreeable reactions induced by the drug itself. Since use of the drug is persisted in until full clinical improvement is definitely established, it is interesting to note, as a good measuring rod, that it was employed for an average of four and one half days in the series of 386 cases of Fhppin *et al* (1941) at the Philadelphia General Hospital.

Types of Pneumonia Affected—These chemotherapeutic agents are of much wider application than serum because they seem to be equally effective in all the 32 types of pneumococcus lobar pneumonia whether the case be of primary or postoperative or post traumatic or other secondary origin. In the primary streptococcic and staphylococcic pneumonias the newer drugs in the series are also effective, Carey (1941) has reported astonishingly fine results in pneumonias of this sort in infants and children, though he did not attempt in all instances a sharp distinction between lobar and bronchial involvements. In the frank bronchopneumonias although brilliant results are many times achieved, it is more difficult to assess the results in general, for, as Kinsman and Moore (1941) well emphasize, these pneumonias are so frequently terminal events in other conditions themselves tending toward fatality that it is difficult to know just how much has been accomplished with drugs. But Plummer (1940) says that a highlight in his recent experience has been the observation of responses in some of the most unfavorable pneumonias complicating heart disease, bronchiectasis, asthmatic bronchitis, emphysema, and old age. In infancy and childhood the drugs have a fine record even though many of these pneumonias occur as complications of other acute illnesses. Plummer and Liebmann (1940) find the pneumococcus bacteremias which are usually fatal if untreated, responding dramatically to these drugs and indeed feel that such a bacteremia, persisting after adequate sulfonamide administration is usually due to a focus such as vegetative endocarditis. In mixed infections, particularly if Pfeiffer's bacillus (*Hemophilus influenzae*) is present results have not been striking but the number of cases so far reported has been small. In infections with Friedlander's bacillus (*Alebsiella friedlanderi*), Finland (1940) says that the results have upon the whole been discouraging though Solomon (1940) reported satisfactory responses in a very small series of cases of the chronic form of the affection which sometimes supervenes in the few patients who survive the acute attack. In the recently described virus forms of pneumonia sulfonamide therapy has failed.

Effect upon the Incidence of Complications—Complications are certainly being seen much less frequently in the new chemotherapeutic era, but in the nature of things we shall probably not ever be able to prove the point sharply with statistical evidence.

Prospects for the Future—The development of this group of drugs has marked a great advance in the therapy of pneumonia but it seems to me that two points are worth emphasizing here one is that we are likely in the years immediately before us to lose track somewhat of the prevailing types and severity of pneumonia because so many unrecorded cases are going to be treated in the home (Flippin *et al* 1941 say that higher mortality rates than heretofore may be expected from hospitals because only the most severe cases will be brought in) and the other is that as pointed out by Plummer (1940) we are likely to see sequelae now that were unknown before because the patients who might have developed them in an earlier day all died

Sulfonamide Toxicity—See the separate chapter on this subject at the end of the book

Sulfathiazole—A large number of authoritative studies have fully established this drug as superior to sulfapyridine in the pneumonias it will be necessary to cite the evidence from but one representative report Flippin *et al* (1941) of the Committee for the Study of Pneumonia Philadelphia General Hospital treated 400 adult patients 200 with sulfapyridine and 200 with sulfathiazole with the following results

(a) Sulfapyridine appeared to act more rapidly than sulfathiazole as judged by the fall in temperature but the duration of chemotherapy the incidence of complications and the average hospital stay were the same for the two treated groups

(b) The severity and frequency of nausea and vomiting were significantly less in the sulfathiazole than in the sulfapyridine-treated group other toxic manifestations being infrequent and comparable in the two groups The superiority of sulfathiazole lies in this then that it is just as effective as sulfapyridine and much less likely to provoke nausea and vomiting which have always been serious objectionable features of sulfapyridine employment

One may use the dosage of Flippin *et al* as model in adults an initial dose by mouth of 45 grains (3 Gm) followed by another dose of the same size in four hours then 15 grains (1 Gm) every four hours—unless severe signs of toxicity develop—until the temperature remains normal for forty-eight hours and the patient shows evidence of clinical improvement When it is felt that the blood level of sulfathiazole should be raised as rapidly as possible sodium sulfathiazole may be given intravenously in 5 per cent concentration in sterile distilled water or sterile physiologic saline solution (administer in dosage of 0.06 Gm per kilogram body weight) Finland *et al* (1941) in their very considerable experience at the Boston City Hospital have rarely found it necessary to give more than three such intravenous injections at eight to twelve-hour intervals (usually cutting in half all injections after the first) before beginning oral therapy

The dosage in infants and children is 1 to 1½ grains per pound of body weight per twenty four hours (0.06 to 0.1 Gm per 450 Gm) The practice of Wagoner and Hunting (1941) is that usually followed namely to give as an initial dose one half the calculated twenty four hour dose The following is a simplification of the schedule of Stoesser and Mooney (1941) by which one can determine in terms of the commercially available 0.25 and 0.5 Gm tablets the four hour dosage for children of average size for their age

Age	Tablets		Interval (hrs)
	0.25 Gm.	0.50 Gm.	
Below 6 mos	$\frac{1}{2}$	$\frac{1}{2}$	4
6 mos-1 yr	1	$\frac{1}{2}$	4
1-3 yrs (incl)	$1\frac{1}{2}$	$\frac{1}{2}$	4
4-6 yrs (incl)	2	1	4
7-9 yrs (incl)	3	$1\frac{1}{2}$	4
10-12 yrs (incl)	4	2	4

In the study of Flippin *et al* in adults, above mentioned it was found that on inadequate dosage from the standpoint of clinical response there was an average sulfathiazole blood level of about 5.5 mg per 100 cc but satisfactory responses occurred at all levels ranging from less than 2 mg to 15 mg per 100 cc, this has been common experience. Increase in toxic manifestations, particularly nausea and vomiting did pace the higher levels however.

Because acetyl sulfathiazole is likely to precipitate in concentrated urine, it is necessary to administer plenty of fluid while giving this drug. Long (1940) says that in adults the urine output should be kept at 1000 cc or more per day, other men like the rule 'intake 3000 cc or more output at least 1500 cc'.

Sulfapyridine—This drug having been practically completely superseded by sulfathiazole it is not necessary to do more than mention the following points with regard to it.

(a) Dosage is about identical with that of sulfathiazole except that the first large dose is not repeated before starting with the smaller doses.

(b) Optimal blood levels have not been established for the drug, Flippin *et al* (1941) found the average figure to be 8.2 mg per 100 cc in their cases (nearly 3 mg higher than sulfathiazole), but this figure bore no regular relationship to therapeutic effect.

(c) Fluids are to be 'pushed' when using this drug just as when using sulfathiazole and for the same reason (see above).

Sulfadiazine—This, the newest of the sulfonamides to have extensive trial, has certainly gotten off to a good start. At the time of this writing, in February 1942, I have before me three significant reports: that of Finland *et al* (1941), who treated 316 pneumonias of which 178 were pneumococcic, that of Dowling *et al* (1941), who treated 115 pneumococcic pneumonias, and that of Flippin *et al* (1941), who treated 200 pneumococcic pneumonias, 100 with sulfadiazine and 100 with sulfathiazole as controls. There seems no doubt from the reports that at least in the experience of these competent observers the new drug is fully as effective as sulfathiazole and perhaps even less toxic in that it seems to cause less nausea and vomiting. A further point in its favor is that it is acetylated to a less extent than is sulfathiazole, and the acetylated product is less soluble in urine than is the comparable sulfathiazole product, therefore, at least theoretically, it would be less likely to cause disturbances in the urinary tract (see section on Sulfonamide Toxicity at end of book).

The dosage of Finland *et al* may serve as model. Patients were given an initial dose of 2 to 4 Gm (30 to 60 grains) and then 1 Gm (15 grains) every four hours until the drug was discontinued which was usually three to five days after the fever had subsided entirely. In some of the severest attacks an initial dose of 5 Gm (75 grains) of sodium sulfadiazine was given parenterally.

in physiologic saline the solution being introduced either intravenously or by hypodermoclysis—in the former case in 100 cc of saline, in the latter in 1000 cc

The average blood concentration of sulfadiazine in the cases of Flippin *et al* was 8.6 mg per 100 cc, it is apparently notably easy to maintain high concentrations of this drug because it is rapidly absorbed and relatively slowly excreted

SERUM IN SELECTED CASES

Type specific antipneumococcic serum was before the profession for many years prior to the advent of the sulfonamides but it never came to be widely used for the following reasons (a) the relatively small proportion of patients considered suitable for this type of therapy (b) the general cumbersomeness of the procedure and the lack of reliable typing facilities in many nonmetropolitan areas (c) the unwillingness of many physicians to impose the added burden of possible serum reactions upon their patients (d) both the obtaining of the material for typing and the administration of the serum were particularly difficult in infants and children and (e) expense. But its effectiveness was undoubted in those instances in which all the criteria for its employment were fulfilled.

Nowadays there are available a number of careful studies (such, for example, as those of Dowling *et al*, 1949; Bullowa *et al*, 1940; Carey, 1941, and Haviland, 1941) indicating that the combined use of serum and chemotherapy is provocative of somewhat better results than can be obtained with chemotherapy alone. Nevertheless none of the leading students of pneumonia in the United States today are advocating the routine employment of the combination. All of the above-cited workers (Haviland alone excepted) who feels that one dose of 100,000 units of serum seems to be indicated in every case after drug administration has begun) plus many others including the members of the Committees which recently advised the National Research Council with regard to the treatment of pneumonia in the armed forces favor a procedure which may be simply stated as follows: Whenever possible take sputum for typing and blood for culture before starting the administration of the drug; then administer homologous serum (rabbit preferred) in addition to the drug under these circumstances: (a) if patient is in fourth day or later when first seen; (b) if several lobes are affected and the process is rapidly extending; (c) if there is bacteremia of a high degree; (d) if the patient is pregnant or in the early weeks of the puerperium; (e) if the pneumococcus is of Type III, the most dangerous of all; (f) if satisfactory response to the drug is not obtained in thirty-six or at most forty-eight hours.

In view of the fact that serum is now so little employed I shall confine myself to a very brief outline of the practical aspects of its use.

(a) *Concentrated rabbit serum* is now preferred to horse serum; it can be given in smaller volume for a given unitage; it is considered possibly able to penetrate tissues better because of the smaller size of its molecule; individuals previously sensitized with horse serum may be given rabbit serum; higher potencies can be obtained in some of the Types than is possible in horse serum; rabbit Type XIV serum may be safely given which is not true of horse serum of this Type.

(b) I quote the report of the Committees to the National Research

Council (1941) for a condensed statement of preliminary tests for hypersensitivity

"Two tests for serum sensitivity are available, and it is frequently desirable to use both. The first consists of the intracutaneous injection of 0.1 cc. of a solution of the serum diluted 1 to 10 in sterile physiologic solution of sodium chloride. The reaction is positive if at the end of twenty minutes the wheal at the site of the injection has enlarged to the size of a nickel and has an area of redness about it. (I do not know how many agree with Volini and Levitt [1939] of Cook County Hospital who consider this test often gives false positive reactions with rabbit serum.) The second test is the conjunctival test. This consists of instilling 1 drop in a 1 to 10 dilution of the serum in sterile physiologic solution of sodium chloride inside the lower eyelid of the patient. If redness and swelling of that eye appear within twenty minutes, the reaction is positive. A positive reaction can be countered easily by instilling 1 or 2 drops of a 1 to 1,000 solution of epinephrine hydrochloride inside the lower eyelid, a procedure which should be followed with all positive reactors in order to prevent the rare instances of corneal ulceration. These tests are interpreted as follows: If the ophthalmic and cutaneous reactions are negative, then antitoxin may be given by any route. A definite wheal like reaction, with surrounding erythema, indicates cutaneous sensitivity. A positive ophthalmic reaction with or without a positive intradermal reaction indicates a probable systemic reaction. Serum should never be given if both the ophthalmic and the cutaneous reactions are positive and should be used only with the greatest of care if either the ophthalmic or the cutaneous reaction is positive."

Of course serum should not be given to any patient with a history of asthma, hay fever, food sensitiveness, urticaria or angioneurotic edema, or to one who admits serious reaction to any previous serum injection.

(c) *Administration* is intravenous except to infants, in whom it is given intramuscularly. It is customary to give the first 0.5 to 1.0 cc. as a test dose, diluted with 0.9 cc. of saline and injected very slowly while watching the patient's color, pulse, etc. Some follow this rule. If after five minutes the pulse has risen 20 beats or the blood pressure fallen 20 points the patient should be considered sensitive, if, however, there has been no reaction in one hour after the preliminary dose the full dose may be injected, preferably at a rate not to exceed 1 cc. per minute, a syringe of epinephrine (adrenalin) solution should be at hand in any case.

(d) *Dosage*—The Committees reporting to the National Research Council (1941) have recommended an adult initial dose of 200,000 units if the attack is in its early stages, 300,000 units if in an advanced stage, subsequent doses of 100,000 units every eight hours if necessary. This is of course high dosage but it is assumed nowadays that the serum is being given only when there are strong indications, as listed above, for its supplementary employment with chemotherapy. For children the dosage is reduced somewhat. Carey (1940) gave from 30,000 to 60,000 units from infancy up to twelve years, but many men feel that above the age of two the dose should be at least 100,000 units, and 150,000 units if given intramuscularly. A few men are now using the intracutaneous polysaccharide test of Francis as a guide to dosage, feeling that there is no certain clinical index of the point at which an adequate amount of serum has been given. Edwards *et al.* (1939) and Wood (1940) have been especially interested in this method lately, but since its application requires special preparations not generally available, and the reaction is not serviceable at all in about 10 per cent of instances, I shall not describe it here.

(e) *Reactions*—In the acute allergic reaction, occurring during or shortly after the administration, the patient becomes anxious, dyspneic, flushed, and

cyanotic, and the pulse is rapid and weak. Often there is tightness in the chest and a desire to vomit, urinate and defecate. Epinephrine (adrenalin) controls all but a very small percentage of these cases. Chills and fever (the so-called 'thermal reaction') may occur within fifteen minutes or after an hour and a half or more, adrenalin is of no use here and in some instances the usual treatment for hyperpyrexia may have to be instituted and often it is necessary to treat the patient for shock also before the incident is over. It is said that acetylsalicylic acid (aspirin), given before injecting the serum, reduces the incidence of thermal reactions. Beeson and Hoagland (1938) obtained immediate cessation of the chill by giving 10 to 20 cc. of 10 per cent calcium chloride very slowly intravenously, there was no relief if the patient had previously received adrenalin. Urticaria, of either the small or giant variety is seen relatively rarely with the refined serums now in use, adrenalin usually controls it. Serum sickness may occur in four to twenty-one days after an injection but is usually mild nowadays.

(f) *Contraindications*—In addition to allergic individuals and those who have previously had a severe reaction, serum should not be given to old and debilitated patients, to those in shock or with congestive heart failure, to those with acute pulmonary edema or those already moribund. For patients in whom a focus such as an empyema, has been established it is wasted if given before the institution of surgical drainage.

NEW QUININE SUBSTITUTES

Quinine is highly bactericidal for the pneumococcus in the test tube but its use in clinical pneumonia has never become established outside the practice of a few men. Ethyl dihydrocupreine (optochin) was very effective but had to be abandoned because of its penchant for causing blindness. The basic salt (optochin base) was much less prone to attack the optic nerve but even it was considered by most men too dangerous for general employment. Recently, however, an entirely new quinine substitute, hydroxyethylapocupreine, is being given a thorough study by MacLachlan and his associates (1937-1941) in Pittsburgh. They have treated 494 patients with this drug and have found it fully as effective as the sulfonamide (sulfapyridine) with which they compared it. The only evidences of toxicity have been occasional nausea and vomiting, there have been no visual disturbances. The preparation used is hydroxyethylapocupreine base, in adult dosage of 15 grains (1 Gm.) every three hours. It is felt that persistence in administration beyond four days is not necessary in cases in which favorable response has not been obtained. Further studies with this drug will certainly be awaited with much interest.

OXYGEN THERAPY

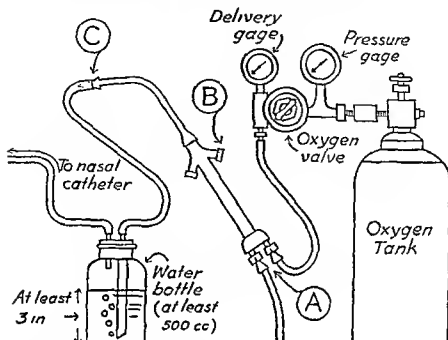
The chief reasons in the past for the administration of oxygen in pneumonia were that (a) proper aeration of the blood was difficult in the normal atmospheric content of oxygen because shallow breathing did not permit full ventilation of the lung and consolidation and edema fluid prevented ready diffusion of oxygen into the capillaries, (b) cardiac effort is greater when there is a diminished supply of oxygen and (c) the presence of fever calls for increased oxygen consumption. It has been felt that in addition to cyanosis (not seen in the very anemic individual even though there is a quite high

relative anoxemia, and in circulatory failure sometimes masked by pallor), oxygen deficiency may be manifested by considerable gastro intestinal, respiratory, circulatory, and central nervous system disturbances—and that, therefore, in most cases of pneumonia the therapeutic administration of oxygen in a concentration of 50 to 60 per cent had best be begun as soon as possible. Indeed, for a good many years the routine administration of oxygen in pneumonias has been a matter of course in many hospitals with the wealthier type of clientele and a good many physicians have felt they were extremely remiss if they did not use the gas in every case even though the apparatus had to be hauled to the home. However, so far as I am aware, there has never yet been published any satisfactory proof that oxygen therapy is life saving no matter how much better the patient may look and possibly feel under its influence. It is terribly expensive therapy, and my own feeling is that it will have a hard time holding its own in these days of brilliant success with the sulfonamides. Possibly oxygen plus the sulfonamides will save some patients that the drugs alone would have allowed to die—but I'd like proof in a fully controlled study, of that!

In place of the completely enveloping tent, which is greatly objected to by many patients and is extremely difficult to operate, numerous hospitals have one or the other of the several types of face mask which have been devised (Campbell, 1936-38, Barach, 1937, Lombard and Nelson, 1939, Christie, 1938). Each of these has its advocates of course and they are probably all fairly satisfactory. The latest development in this field is the "B.L.B." apparatus (Boothby *et al*, 1940) perfected at the Mayo Clinic, it consists of a rebreathing bag as well as a mask which is tightly strapped over the nose, or both the nose and mouth, and I understand many patients do not like it. It seems that most oxygen is still administered, whether in homes or hospitals, by either the nasal catheter or nasal inhaler methods.

Nasal Catheter Method—A special nasal catheter may be used but the ordinary urethral soft rubber catheter No. 10 to 14 French, is just as good provided that several holes are cut in it at intervals of $\frac{1}{2}$ inch. Obtain a rough idea of the depth for insertion by measuring with the catheter the distance from the external nares to the tragus of the ear, lubricate with petrolatum (not light oils or jellies which quickly dry), turn on the flow to a rate of 5 or 6 liters per minute and gently introduce the catheter into one nostril until the tip is discernible at the level of the uvula. (Waters *et al* [1936] prefer to continue the slow introduction until the patient is seen to take a swallow of the oxygen and then to withdraw it just to the point where swallowing is no longer seen.) The catheter is then supported and held in place by bringing it up over the nose and fastening with adhesive tape to forehead or cheek. The advantage of using only one catheter at a time is that a fresh catheter can be introduced into the other nostril before the old one is removed, a fact of great importance in a patient attuned to oxygen concentrations higher than normal, replacement should take place every twelve to twenty four hours, more often if the quantity of mucus necessitates it. With the catheter method Barker *et al* (1934) and Rovenstine *et al* [1936] have found that a 6 liter flow will produce an alveolar oxygen concentration of only 30 to 35 per cent and that to obtain the desirable 50 to 60 per cent required a flow of 10 to 12 liters. It will require spraying of the nasal cavity and oropharynx every hour with liquid petrolatum to make

DIAGRAM AND TABLE FOR CONVERSION OF OXYACETYLENE WELDER INTO APPARATUS FOR DELIVERY OF THERAPEUTIC OXYGEN



At A disconnect tube from acetylene tank

At B open the valve fully and leave it open

At C read the standard size number of the welding tip

Apply to the Table to learn what the oxygen delivery gauge must read for each size welding tip in order to deliver the desired number of liters per minute to the patient

Pounds pressure shown on delivery gauge	Liters of oxygen delivered through welding tips *				
	No 1	No 2	No 3	No 4	No 5
2	2	2 25	3 25	3 75	4
3	3	3 5	5	5	6
4	3 75	4 25	6	6	7
5	4	5	6 75	7 5	8
6	4 5	5 5	7 75	8	9
7	5 25	6	9	9	10
8	5 75	6 5	9 75	10	11

* I am very grateful to my former technician, Mr Oscar Ugi who derived these figures for me

these higher flow rates tolerable to most patients. It should be noted that Roventine achieved 50 per cent concentration with only a 6 liter flow by employing the Waters technic for placing the catheter (see above).

Nasal Inhaler Method—The inhaler is a metal Y tube (malleable so that it can be bent for individual adjustment) with plugs on the two ends of the Y much like those on the earpieces of a stethoscope. It is so shaped that when the plugs are in the nostrils the stem of the Y lies up over the middle of the forehead where it may be fixed in place by adhesive or a suitable strap. When using the inhaler about the same alveolar oxygen concentration is accomplished at a given flow rate as with the nasal catheter (see above), children will rarely tolerate a flow of more than 2 liters by either method. Even the most cooperative patient often cannot refrain from pulling the inhaler plugs out of place because of the irritation they cause.

Oxygen Supply—Tanks of commercial oxygen as used by welders are just as satisfactory as and cheaper than so-called 'medical' oxygen. The larger the tank the cheaper the unit of oxygen, the 'large' 220 cubic foot tank (2000 pounds pressure) will deliver 6000 liters of gas—enough for sixteen hours at 6 liters per minute, or eight hours at 12 liters per minute. The apparatus in use in hospitals and available on rental for use in the home in large cities has pressure and flow gauges and conducts the oxygen through a humidifier en route to the nasal catheter. In the accompanying diagram and table I have sought to indicate how the ordinary oxyacetylene welding outfit (available in practically every auto repair shop throughout the country) may be converted very quickly into a satisfactory machine for the regulated delivery of oxygen to a patient. One should be very careful to keep oil of any sort away from all parts of such an apparatus.

NURSING MEASURES

The patient should be put to bed in a well ventilated room but I do not see the sanity of forcing upon him and his nurse the extreme exposure still advocated by a few. Many physicians of long experience insist that, whether exposed or not, the arms, shoulders and chest should be continuously swathed in a flannel jacket which can be easily made extemporaneously, with the quick results being accomplished by the sulfonamides nowadays. I imagine that very few will any longer employ this measure which indeed was given up long ago in most hospitals where pneumonia is being actively studied. The use of bed pan and urinal should be enforced of course but having thus conserved the patient's strength it is doubtfully advisable to waste it again by permitting him to move about very much in order to facilitate the percussion and auscultation of his back. If the mouth is kept clean the patient will be more comfortable than when it is dry and dirty and he will also eat and drink with more relish, possibly too the danger of superinfection may be lessened. The best way to keep the mouth clean is to wash it with alkaline aromatic solution N F and then apply a small amount of petrolatum to the tongue and cold cream to the lips. Some patients also enjoy having the nasal passages cleaned out with a spray (see under Common Cold). External hydrotherapy should not be employed save for a daily, quietly given, tepid sponge bath, and indeed the omission on the worst days of even this part

of the sacred nursing ritual may be highly advisable. As a matter of fact the sole reason for giving this bath is to cleanse and refresh the patient. If it tires and irritates him—as is very often the case when it is combined with a bustling bed-changing bout—why persist in it? No one has yet died from lying in bed for a few days without a bath or a stem-to-stern change of linens. Lever itself is advantageous most likely—but if it becomes excessive so that the patient's nervous system begins to be disturbed then the antipyretic drugs will control it much more safely than rigorous cold bathing procedures. I like very much Hall's (1936) reminding us of the old soldier's notice pinned on the bed: "Too sick to be nursed today."

And when the corner has been turned? Two weeks in bed after the temperature is permanently normal and a very gradual resumption of accustomed activities. I am aware that the sulfonamides are getting em out earlier—but there are n good many wraiths stalking the streets too—who in my opinion should still be in bed.

DIETETICS FLUID AND CHLORIDE ADMINISTRATION

The course of an attack of pneumonia from diagnosis to defervescence or crisis being usually only a few days there is no need to worry if the patient's total caloric intake falls somewhat below the normal. Chief concerns should be that he is not given large quantities of food at the usual long intervals but instead is offered small amounts frequently and that the total amount of fluid taken by mouth (and vein if intravenous dextrose is being given) is 3 to 4 quarts (liters) daily—the use of the sulfonamides should not be allowed to influence this fluid intake one way or the other. Most individuals lose completely their desire for solids but are very thirsty; they likewise sometimes prefer salted to plain water. This latter is considered fortunate since it has been shown that the disease is often characterized by a considerable diminution in plasma chlorides which would make the administration of sodium chloride theoretically advisable. Haden has supplemented the food chloride by 6 to 24 Gm. salt daily. Sunderman, 15 to 30 Gm. It is highly desirable that as much of the fluid as possible be taken in the form of fruit juices (orange, lemon, pineapple, grape or grapefruit) flavoring them with milk sugar (lactose) or with dextrose instead of ordinary sugar (sucrose) is of advantage since additional calories can thus be added without too much sweetening. The following mixture (which I present as a formula) has enabled Wilder and Drake to give chlorides, fruit juice, dextrose and water all in one drink:

Sodium chloride	1 Gm.
Dextrose	50 Gm.
Orange juice	200 cc.
Water	400 cc.

In the dietary outline which follows the patient will obtain 50 Gm. of protein and 1800 or more calories—the latter depending upon what additional amount of fruit juice (or of the above mixture, preferably) he will care to take.

8 A M	Fruit juice and cooked or packaged cereal with sugar and cream
10 A M	A glass of milk or buttermilk
12 M	Fruit juice A glass of milk or buttermilk Soup made one half of strained vegetables, one fourth of milk and one fourth of cream
3 P M	Fruit juice A glass of milk or buttermilk A soft boiled egg (Or the milk and egg may be substituted by eggnog)
6 P M	Fruit juice Milk and egg (if eggnog was taken at 3 P M) or eggnog (if milk and egg was previously taken)
8 P M	A glass of milk or buttermilk

Fruit juice preferably prepared as in the chloride and dextrose formula, may be given several times during the night it should be presented with some persuasion at least twice if the patient is awake The patient is not to feed himself but is to use a glass tube for the liquids and the semisolids are to be spoonfed by the nurse

After the crisis is past return should be made toward the normal diet by adding buttered toast and small servings of pureed vegetables chicken or red meat and potato to the above diet

SYMPTOMATIC TREATMENT

Cough—Though this is a beneficent measure designed to rid the oropharynx of foreign material which is choking them it is sometimes excessive Whenever cough is in the least degree exhausting the patient attempt should be made to control it by such measures as have been described in the discussion of the common cold (see Index)

Pain—The pain in the side is often satisfactorily controlled by judicious employment of adhesive plaster and a hot water bag occasionally an ice bag will give more relief but it should probably not be applied more than two hours consecutively If the pain is very severe and causing considerable restlessness the opiates must be used for its relief Codeine, 1 grain (0.06 Gm), may suffice if not, morphine $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.008–0.015 Gm), or dilaudid 1/48 to 1/32 grain (0.0013–0.002 Gm), may be given but the single dose perhaps had best not be repeated because of the possibility of increasing abdominal distention and decreasing pulmonary aeration Sometimes also the patient becomes quite ill, even to the point of vomiting several times, a few hours after taking morphine perhaps more rarely after dilaudid

Diathermy sometimes induces great relief, and it is now the consensus that it has no effect other than that Reimann (1939) says that in his experience a hot sandbag or water bottle provides just as much comfort at much less cost Schnur (1939) has sought to relieve pleural pain by local injection of procaine (novocain), infiltrating 5 to 10 cc of 2 per cent solution intracutaneously subcutaneously and into the region of the pleura, most of it being injected deeply immediate relief was obtained in all 32 cases and in 21 of them the relief was permanent Artificial pneumothorax will also relieve pain and is said to be indicated in a few instances

Restlessness and Delirium—Restlessness and sleeplessness must be overcome since peace of mind and body are of the utmost importance to the patient. If opiates are not being employed for the control of cough or

pain they may be required to secure bodily quiet. It is well however first to try a milder sedative. Delirium may appear very suddenly even in a patient who has not been previously restless and cause such violent exertion as to induce sudden death. Bullown (1933) reported the satisfactory use of avertin in these cases 60 mg (1 grain) per kilogram (2 2 pounds) by rectum. When the patient is very violent and rejects much of the drug he uses a barbiturate in addition—0.005 Gm (1/12 grain) of dial with urethane per kilogram (2 2 pounds) intramuscularly or intravenously. The study of King and Moersch (1941) indicates that there is no danger in using the barbiturates in ordinary sedative dosage when the sulfonamides are being employed.

Tympanites—Distention of the abdomen with gas is a symptom which is distressing and serious for it oftentimes adds to the respiratory embarrassment. Fortunately in these days of sulfonamide therapy it does not occur nearly so frequently as formerly. It is best treated by prevention that is to say by cleaning out the lower intestinal tract by a 1 per cent sodium bicarbonate enema as soon as the case comes under observation. In the opinion of many men this enema should be repeated at least every twenty four hours a rectal tube being used during the interim but if the patient is in poor condition Cornwall (1936) opposes bothering him with such routine manipulations unless the tympanites is intractable. Bethea gives $\frac{1}{2}$ to 1 ounce (15 to 30 cc) of liquid petrolatum every night and an enema only if needed because of distention. When distention is severe and persistent turpentine stupes may be employed as in the following method.

First place a blanket under the patient in such manner that it can be drawn across the abdomen in double breasted fashion. Anoint the abdomen with petrolatum (vaselin). Then spread a Turkish towel over a small pan and place in the center of it another Turkish towel folded to the size of the abdomen. Now pour over this second towel boiling water to which has been added 1 teaspoonful of turpentine to the quart take up the two ends of the first towel and quickly wring the stupe nearly dry by twisting these ends in opposite directions. Then remove this stupe which is so hot that you can only hold it by rapidly shifting hands from the wringing towel and place it upon the abdomen—and lift and replace lift and replace until the patient can bear the heat then draw a layer of the blanket tightly across the abdomen from each side—and you have done it! The stupes must be applied every five minutes until relief is obtained and in addition $\frac{1}{2}$ to 1 cc of pituitrin or pitressin may be given every twenty minutes for 2 or 3 doses.

The following carminative enemas are of value (1) $\frac{1}{2}$ to 1 drachm (2–4 cc) of turpentine emulsified by beating with the white of an egg and added to a quart of water (2) One to 3 drachms (4 to 12 cc) of the emulsion of asa fetida added to a quart of water this latter preparation is esthetically very objectionable.

Goldman and Cohen (1936) have employed in combination the laxative action of saline cathartics and the mechanical action of continuous rectal suction siphonage.

When dilatation of the stomach occurs the situation is indeed serious though some men attempt to introduce a Levine tube or to employ the Wangenstein suction apparatus.

Circulatory Disturbances—In many cases of pneumonia of moderate severity the pulse is no more rapid throughout than is consonant with the

elevation of temperature. Also it not infrequently occurs in fatal cases that the failure seems to be entirely respiratory, pulse rate and force remaining quite good almost to the end. Again we have to date no blood pressure studies which can be accepted as proof positive that early primary circulatory failure is *typical* of this disease. However it is undeniably true that there is some degree of circulatory failure in most cases and that in many fatal instances the death seems to be primarily a circulatory one. We now know definitely that this failure is a peripheral circulatory one though the mechanism of the vasodilation is not yet understood. Therefore since it is peripheral vascular relaxation rather than heart failure with which we have to deal the situation is a very serious one indeed for we have no drugs that are really satisfactory aids in such a situation. The Cornell and Rockefeller Institute group (Wyckoff *et al.* 1930; Niles and Wyckoff, 1930; Cohn and Lewis, 1935) conclusively showed that digitalis is not indicated, indeed should auricular fibrillation supervene and necessitate the use of the drug it should be employed in dosage considerably lower than would routinely be employed in such cases. Caffeine, camphor, metrazol, coramine, strychnine? They have all been tried and without much success. Eggleston (1941) considers adrenalin to be contraindicated.

Blood Concentration—(a) *Venesection*.—A number of years ago Underhill and Ringer studied a series of 43 cases of influenzal pneumonia from the standpoint of blood concentration and were able to show a distinct relationship between the gravity of a given case and the extent of the abnormal concentration of the blood. Upon theoretical grounds they advocated the withdrawal of blood by venesection and the introduction of fluid into the body, but were unable to carry out the treatment in many cases. It may be surprising to some to learn that a definite and logical basis exists for the letting of blood in pneumonia, a procedure which was at once the darling of our forefathers' hearts and the object of their greatest therapeutic abuse. A number of independent investigations in pointing out the reactive leukocytosis, the coagulation changes, the hyperglycemia and the mobilization of antibodies indicate that it may be considered as a form of protein therapy. Also Petersen and Levinson in reviewing the work of Lord and Nye and others by which it was shown that a ferment-antiferment balance exists in the pneumonic exudate, reasoned that following venesection there may occur an alteration in this balance by reason of the withdrawal of some of the antiferment when fluid is rushed from the tissues into the vascular bed. To understand the logic of this it must be borne in mind that the ferments which are looked upon as overcoming the organisms are believed to be shed by the dying leukocytes at the focus of the infection. Conner (1941) feels that in some instances of pulmonary edema occurring early in the disease venesection may be justifiably resorted to. Eggleston (1941) agrees.

(b) *Dextrose*.—Since there is no reason to restrict fluids because the sulfonamides are being given, intravenous infusions of dextrose solution are holding their own very well in the new chemotherapeutic era. The most obvious advantage of dextrose therapy of course is that while supplying fluids it also makes available in a short time a large quantity of food material which does not have to undergo preliminary digestive processes.

Pulmonary Edema.—This is often a terminal event and nothing can be done. Sometimes, however, it occurs early in the attack. Venesection (see

above) may be performed in these cases or one may give concentrated dextrose solution as recommended by Bullowa some years ago 100 to 150 cc of 50 per cent dextrose solution intravenously at intervals of several hours attempting to force the lungs to give up their fluids in order to dilute this concentrated solution. One may attempt to overcome excessive loss of fluid into the urine by giving insulin to help metabolize the dextrose a little less than 1 unit for each 2 Gm of dextrose subcutaneously at the close of the intravenous injection. Concentrated sucrose solution (see Index) may also be used. Barach *et al* (1938) have proposed a type of positive pressure respiration for some of the acute pulmonary edemas but I have not heard of this method being employed in the pulmonary edema of pneumonia.

PROPHYLAXIS

Vaccines made from killed pneumococci or from pneumococcus polysaccharides have been tried as prophylactic agents in institutions particularly those harboring the aged but the findings are by no means convincingly in favor of their present employment. The paper of Kaufman (1941) will lead the interested reader into the literature.

POLIOMYELITIS

(Acute Anterior Poliomyelitis, Infantile Paralysis)

Poliomyelitis is an acute infectious disease which typically attacks young children only those under six years of age being in the most susceptible group with the exception of infants under six months who seem to be immune however adult cases are reported less rarely now than formerly. The most dreaded symptom paralysis is caused apparently by both a toxic and a hyperplastic assault upon the anterior horn cells in the cord. The causative organism a filtrable virus seems to go through avirulent and virulent periods during both of which many mild so-called abortive cases occur in which there is little or no paralysis though immunity is conferred by such an attack during the latter periods the disease tends to become epidemic—pandemic too at least to the extent that a large number of local epidemics may occur at about the same time scattered throughout the world. The study of Toomey and August (1933) very interestingly associated this seasonal epidemicity with the harvest time for perishable fruits and vegetables in various parts of the world several other observers have also thought that there was some evidence of connection between fresh fruits and the incidence of infection in epidemics which they studied. The obvious conclusion from such an association would be that the causative organism is ingested and gains access to the nervous tissues through the gastrointestinal tract as many now feel to be the case since Trask and Iaul (1938-41) and their associates have demonstrated the virus in the stool and in sewage sampled in the vicinity of isolation hospitals. Also the fact must not be overlooked that such seasonal periods may merely coincide with the height of activity of some

hitherto unsuspected or at least unconvicted insect vector (recent work redirects attention to the common housefly) There has been some speculation on the possibility that one or several of the lower animals may act as the great reservoir for the virus The majority of students of the disease however, seem still to feel that poliomyelitis is spread by nasal droplet infection from active and carrier cases, and that the virus enters the nasal mucosa and travels centrally along the axis-cylinders of nonmedullated nerves It has never been possible to establish the validity for the human of the observations made of the experimental disease in the monkey, it is still too early for us to know what will result from the recent experimental establishment of infection with this virus in the cotton rat, white mouse and guinea pig

The early symptoms of poliomyelitis are "cold in the head," cough, more or less vomiting and diarrhea, fever, and extreme irritability with coincident malaise and restlessness Reluctance to lower the chin, and also the assumption of a peculiar position in the bed may be seen at this stage Then, in severe cases, and either with or without a remission of several hours to several days, the more severe headache and typical flaccid paralysis of some portion of the body appear The bulbar type of the disease has of late been growing commoner relative to the spinal form The course is now usually afebrile, but the child experiences so much pain on being moved that it frequently manifests excessive apprehension when any person approaches the bed The approach of fatal respiratory paralysis is often very horribly foreshadowed by the way in which the patient, with prescient alertness, marshals his forces for the final agony It is felt to be usually true that the higher the cell count in the spinal fluid, the more severe the attack, in the prodromal stage the fluid is clear but under increased pressure

Poliomyelitis is a very ancient disease, it is thought to be represented on one of the stelae of the eighteenth dynasty (1580 B.C.) in Egypt The first modern account of the predominating infantile type was that of Michael Underwood (1784), though many feel that there was some doubt about his cases and that Heine really established the disease as a clinical entity in 1840 Duchenne in 1855, first pointed out that the paralysis is due to definite lesions in the anterior horns of the cord Negroes are thought to be much less susceptible than whites The investigations of Hudson and Lennette (1939) indicate a wide distribution of the virus throughout the world but apparently in tropical regions man can harbor it as a saprophyte for the clinical disease is seldom seen there Relapses and second attacks of poliomyelitis are of rare occurrence

THERAPY

Orthopedic Treatment—The most hopeful single item that has evolved out of all the world's deep study of poliomyelitis is recognition of the fact that, since involvement in the cord is "spotty," there is rarely complete paralysis and ultimate degeneration of the muscle groups involved The meaning of this is that if contractures are prevented during the acute stage of tenderness, and if thereafter muscle training is properly begun and indefatigably prosecuted, the chances of recovery without permanent crippling deformity are really very good But for success to be achieved it is necessary that these things be expertly undertaken at the moment diagnosis is made Therefore the physician's chief bounden duty to the present state of our

knowledge is to call in a qualified orthopedist as soon as it is known that the case is truly one of poliomyelitis. The measures which this specialist will apply with the help of his physiotherapist assistants will comprise principally the following:

(1) By the use of such pillows, splints or other mechanical devices as are necessary the various parts of the body will be placed in physiologic rest at once, alterations in the positions of the parts being made when the extent of the paralysis has become established.

(2) Local circulation is maintained by the application of external heat in the form of hot wet packs or hot baths if these can be given without disturbing the patient. The moist heat seems to hasten disappearance of the painful stage.

(3) When pain disappears massage is begun with possibly immersion saline baths to obtain surface hyperemia but without movement or manipulation of the affected parts even under water.

(4) Gradual increase in force and duration of the massage and then the introduction of passive movements.

(5) Active movement finally begins after careful analysis of the deterrent effects which gravity, friction and atmospheric pressure are likely to have on the movement. The advantages of under water treatment are: (a) The buoyancy of the water counteracts the influence of gravity and friction so that the sense of accomplishment cheers the patient. (b) The wide range of activity also diverts and is inspiring during the protracted treatment. It is worthy of note as pointed out by Hansson (1939) that beside a pool in the Hospital for Ruptured and Crippled in New York there is a plaque which says: "This pool is given to the physically handicapped children that in pleasure they may regain their health." (c) Knowledge of body balance gained under water is helpful to the patient in adjusting himself to walking in braces later.

(6) When the maximum amount of recovery has been accomplished by muscle reeducative measures and the application of braces, operative surgery may be undertaken to accomplish transplantation of muscles and tendons and the eradication of unstable joints by bone fusion.

Kenny Treatment—Currently the system of treatment devised by nurse Kenny in Australia is being studied by orthopedists. Recognition of the importance of muscle spasm as well as of flaccid paralysis seems to be the backbone of this treatment. Immobilization has been abandoned; very great use is made of hot moist packs and the patient is encouraged to attempt contraction of designated muscle groups under guidance. In Minneapolis where Kenny demonstrated the method, Cole and Knapp (1941) were willing to express cautious approval but felt it too early to attempt full evaluation. They did feel, however, that no harm was done the patient. Various other individuals and commissions that have reported their studies of the method are qualified in their approval or wholly opposed. I have heard it said by an orthopedist who had watched Kenny at work in Minneapolis that in his opinion not everything that met the eye there was to be taken at quite face value. He was nevertheless convinced that the therapy of poliomyelitis would be advanced by Kenny's contributions. I understand that the Minneapolis group who have attempted to effect some sort of standardization of the techniques are preparing a report. After its publication it will probably be easy

to achieve an early and true evaluation of the method since the routines employed will then be available for trial by many men

Maintenance of Respiration—I believe that the report of Brahdy and Lenarsky of the cases treated at the Willard Parker Hospital a few years ago still expresses the consensus of what can be accomplished with the *Drinker respirator* popularly known as the iron lung. Analyzing the results obtained in 68 cases they found that proper selection of patients is essential for success since the apparatus was useful only in patients with paralysis of the respiratory muscles due to the lesions of the spinal cord. The patients with injury of the respiratory center who were treated in the respirator all died. Patients whose respiratory difficulty is due to inability to swallow saliva mucus etc should not be treated in the respirator nor should those with only slight evidence of respiratory embarrassment without cyanosis or dyspnea—on this latter point however Wilson (1940) is in disagreement he would have all patients placed in the respirator at the first sign of weakness of the respiratory muscles. *Respirator rooms* in which many patients may be placed and cared for at the same time are operating satisfactorily in the few hospitals in which they have so far been constructed. In England use has been made of the *Bragg Paul Pulsator* an air bag placed around the patient in the manner of a corset and rhythmically inflated and deflated by an electrically operated pump. Study is being made of the jacket type of respirator in the United States also because of the obvious advantages of having the patient more accessible than when enclosed in a respirator of the Drinker type.

Kerr (1939) felt that he saved a patient's life by placing him on a stretcher which was then tilted back and forth about 30 degrees from the horizontal on either side at the rate of twelve times per minute through several days.

Treatment of Difficulty in Swallowing—In Brahdy and Lenarsky's treatment of these cases they relied principally upon the following measures:

(a) *Postural Drainage*—This consisted in elevating the foot of the bed (perhaps as much as 15 to 20 degrees) with the patient's head turned to one side in addition secretions accumulating in the pharynx were removed by suction.

(b) *Duodenal Tube Feeding*—The Levine tube which resembles a urethral catheter with openings on the side at the terminal end comes in sizes 16 14 and 10 French. It is about 45 inches long and is preferably passed through the nose. For use in such feeding Miller (1939) mixed ground and sieved the following ingredients stored the mixture in six portions in the refrigerator and fed one portion every three hours during the day and every four hours during the night to a patient thirteen years old: 20 per cent cream 100 cc milk 1000 cc eggs 6.5 per cent vegetable 180 Gm 10 per cent vegetable 100 Gm cornstarch 30 Gm orange juice 150 cc Karo 96 Gm a small amount of salt. This diet supplied something over 1800 calories per day and was satisfactory from the standpoint of mineral and vitamin content.

Miscellaneous Measures—Spinal drainage has not been reported upon with universal favor but Neal (1941) whose experience is vast says she has often found it of value if there are signs of meningeal irritation she warns of course against its employment in cases of severe bulbar paralysis and in completely asthenic patients. In cases of edema of the brain concentrated

dextrose or sucrose solutions (see Index) may also be tried. The intraspinal administration of epinephrine or ephedrine to relieve edematous pressure on ganglia has been a complete disappointment. Perhaps passing mention should be made however, of Speidel's (1936) use of ephedrine together with glycine (aminoacetic acid) upon the basis of their reported effectiveness in the muscular dystrophies. He gave a teaspoonful of glycine in water after meals, following it in fifteen minutes by a capsule containing $\frac{3}{4}$ gram (0.024 Gm) of ephedrine sulfate. The patient improved rapidly and markedly, but one is bound to remark that in cases of bulbar paralysis, such as this was, progress is usually quite rapid toward death or recovery.

The treatment of bedsores is discussed elsewhere (see Index). When urinary tract infection results from the catheterizations often necessary in protracted cases it is treated just as in other instances (see Index). The use of liquid petrolatum or enemas is often necessitated because of weakness of the accessory muscles of defecation.

The sulfonamides have not yet been shown to have value. Methenamine (urotropin) is worthless. German workers (Kauders, 1937; Klen, 1939) have reported good results with malaria therapy as employed in paresis. Retaa (1937) described a type of treatment resting upon the frequent intravenous injection of hypotonic saline solution combined with graduated spinal drainage but the method is complex and has a number of contraindications, so that its present detailed description here does not seem to me to be warranted.

Convalescent and Adult Serum—The blood serum of individuals who have recovered from an attack of poliomyelitis, as well as that of any normal adult (since in all of us immunity to poliomyelitis increases with advancing years), has had a long trial and has not clearly proved its value. Paul (1941) says "At the New Haven Hospital we do not use serum at present." Neal (1941) reasserts her opinion that it offers "nothing specific." However, such reports as those of Levinson (1936) and of Geiger *et al* (1939) indicate that just possibly its use in preparalytic cases may prevent residual paralysis. Therefore it seems to me that a physician cannot be fairly accused of depriving his patient of the chance to escape having paralysis, a long illness, or death, if he omits the use of serum. But it does no harm surely, and when the parents insist that it be given, the following is the way in which it may be done.

Since the recognition of the fact that the serum may set up sterile reactions in the meninges if injected intraspinally (10 to 30 cc, very slowly, after the withdrawal of an equivalent amount of fluid), that route has been practically abandoned and the injections are now made only intravenously. The dose for children is 50 to 100 cc repeated in eighteen to twenty-four hours and perhaps several times after that; in adults the dose is proportionately larger. Of course a thermal (chill and fever) reaction may occur. Blood should be taken from the donor under aseptic precautions, twice centrifuged to free the serum entirely from red cells, and this serum stored in a cool place. It is best to culture it for sterility, but the addition of 0.2 per cent of tricresol as preservative is permissible. Healthy adults can give from 500 to 750 cc and children of twelve to fifteen from 200 to 250 cc of blood; 500 cc of blood will yield about 200 cc of serum. It is considered that storage at 4° C (about 39° F) for a year is not harmful. Warm the serum somewhat before injecting it.

Intramuscular injection of serum or of citrated blood in average dosage of 40 to 70 cc, has been reported. Of course, whatever action there may be would take longer in developing.

PROPHYLAXIS

Hygienic Precautions—One of the many dark spots in our knowledge of this disease is the fact that we do not understand why a carrier can rarely be definitely indicted by a trail of cases in his wake—that is to say, even in epidemics the cases occur in very spotty fashion. Also if we except 'abortive' subparalytic or perhaps even subclinical cases (whose number of course is unknown) the actual incidence of cases in any given area is very low even though the disease is at the time at one of its epidemic peaks in that area. However, the United States Public Health Service seems still to consider it wise to prevent needless human contacts—as in schools, movies, boys or girls' camps and children's parties during such periods. Since a history of overexertion preceding an attack is often noted it is also considered advisable to curtail children's physical activities. Still there are some who doubt the justification of these measures in view of our present paucity of knowledge, Lumsden (1938) for example feels that possibly their greatest value is as a placebo to public hysteria and demand, and many agree with him.

It has generally been believed that swimming pools and beaches have been centers from which virus is disseminated but careful studies during the Los Angeles outbreaks in 1934 failed to sustain the indictment. Nevertheless as pointed out by Paul (1941) it would certainly seem wise in view of the recent findings earlier referred to to prohibit bathing in any waters which might possibly be sewage polluted. When properly chlorinated it is doubtful if drinking water can be a source of infection. It is still held by a few observers that milk has been occasionally responsible for the spread of cases and they therefore advise boiling it during the time of epidemics.

Tonsillectomy—It is the consensus among leading students of poliomyelitis that tonsillectomy predisposes to the severe bulbar form of the disease. The study of Fisher *et al* (1941) shows that this was true in the last Toronto epidemic as it has been in others in recent years. Ascock (1940), of the Harvard Infantile Paralysis Commission has many supporters when he says that avoidance of tonsillectomy where poliomyelitis is prevalent would undoubtedly prevent the occurrence of a number of cases of the highly fatal form of the disease each year.

Quarantine—The White House Conference recommended an isolation period of three weeks from the onset of febrile symptoms for the patient and other exposed children. Placarding was not recommended.

Vaccines—The use of these preparations has been discontinued.

Adults' Whole Blood—More in Germany suggested in 1930 that since it is very difficult to diagnose the preparalytic stage of poliomyelitis all children under five years of age should be inoculated with their parents' whole blood during an epidemic, repeating the injection after four weeks. The thing has been put to the test in several regions and while controlled studies on a sufficiently large scale to be convincing have as yet to be made such observers as Stokes *et al* (1935) in Philadelphia, believe that study of

the method should be continued both for the sake of the children and to accumulate further statistics. I have seen no further significant studies but Neal (1941) in a recent authoritative review said the results to date 'have not been convincing'. The procedure is described under Measles.

The Nasal Spray—Nasal sprays of whatever sort have not been effective in prophylaxis and in some instances have even been harmful. The hope, like many another that had preceded it, was simply forlorn.

PSITTACOSIS

(Parrot Fever)

This is an acute infectious disease of parrots, parakeets, budgerigars, finches and canaries living in captivity. The study of Pinkerton and Swank (1940) makes it probable that pigeons should be added to this list, the finding of what seemed to be psittacosis in birds of the petrel family, by Haagen and Maurer (1938), combines with this observation to indicate a much more wide spread avian distribution than had been previously suspected. The disease, which is caused by a virus (or possibly, according to recent evidence, one of the rickettsiae) that is oftentimes harbored by apparently healthy birds, can be experimentally transmitted to some of the smaller rodents and to monkeys as well as to birds. The virus has been cultivated *in vitro*.

In man psittacosis occurs usually in house epidemics among persons handling infected birds but it is also possible for direct transmission to occur from human to human as was demonstrated in the Pittsburgh outbreak of 1934. Psittacosis has taken its toll of doctors, nurses and laboratory workers. The two greatest outbreaks have been that in Paris in 1892 to 1895, in which there were 78 cases with 24 deaths and the present pandemic in which at the height in 1930, more than 500 cases were reported on the Continent, in England, North and South America, and the Hawaiian Islands. Small epidemics are still being reported, though with lessening frequency. Cases have been traced to infected birds in shipments from many countries, I believe that in the United States many of the cases have been traceable to birds from California simply because the raising of pet birds has become a large industry in that state.

Children are notably less susceptible to the disease than adults. Mortality seems to average about 20 per cent, but the number of mild and unrecognized cases cannot be estimated of course. There is one recorded instance of a person having a second attack of psittacosis. Though the incubation period is not as yet definitely established, it is believed to be between seven and fourteen days in most instances. The Meyer-Eddie modification of the serum complement fixation test of Bedson is considered to be of great assistance in making the diagnosis.

In man the first sign is usually a chill with subsequent rise of temperature and a pulse rate that is not commensurate with the fever, headache, backache, loss of appetite, white-coated tongue with red edges, abdominal distention, there may be vomiting and either diarrhea or constipation, sometimes, but

not invariably there is leukopenia. Upon this typhoid like picture is engrafted a pneumonia which is atypical in that there are pronounced physical signs of pulmonary involvement often without much sputum or pain in the chest though the cough may be severe. Albuminuria as well as nervous symptoms are often in evidence. The attack may run a course of many weeks the pulmonary symptoms frequently continuing long after the temperature has subsided.

THERAPY

The symptomatic treatment is that of typhoid and pneumonia. In the present pandemic convalescent serum has been tried in doses of 50 to 100 cc daily mixed with an equal quantity of physiologic saline at time of injection intravenously. Smaller doses have been given undiluted intramuscularly. Such evidence as there is in favor of this serum therapy is very inconclusive. Hinshaw (1940) felt that one of the sulfonamides (sulfapyridine) was of value in a case treated at the Mayo Clinic and suggests further trial of these drugs. Koch (1940) in Germany was quite enthusiastic about his results with trypanflavine (acridiflavine) in 7 cases. 10 cc intravenously of a 2 per cent solution daily for three or four days.

RABIES

(Hydrophobia)

Rabies is an acute infectious disease chiefly encountered in dogs though many other animals are susceptible. It is caused by a filtrable virus which is associated with the so called Negri bodies that develop in cells within the central nervous system of infected animals. Webster and Clow first convincingly reported the cultivation of the virus in 1936 though apparently Hamazawa had succeeded at about the same time. A rabid animal biting another animal or a human being transmits the virus in saliva. Not all bitten individuals whether among the lower animals or man develop the disease and it seems possible for apparently healthy animals to harbor the virus as carriers. Once the symptoms of the disease appear however a fatal termination after terrible suffering is certain in both animals and man. In the island of Trinidad in 1931 it was proved that the vampire bat is capable of transmitting the virus between infected cattle and man upon both of which this loathsome fellow feeds. It appears that a belt of this bat transmitted rabies extends down through eastern South America as far as Montevideo.

There is little mention of rabies between the classical description of Aetius a physician at the Byzantine Court in the sixth century A.D. and the keener observers of the eighteenth century such as Boerhaave and his famous pupil van Swieten. The creator of the Vienna clinic Pasteur's first preventive vaccination with the attenuated virus of the disease was performed upon the Alsatian shepherd boy Joseph Meister in July 1885. The specific cell inclusions were discovered in the central nervous system by Negri in 1903-1904. Many years ago Sir Victor Horsley predicted that rabies could be stamped out by the muzzling of all dogs, this has often been put to the test in relatively

small communities (occasionally throughout an entire national domain) and always with complete success, but a world wide attack upon the disease in this way has yet to be organized. Rabies seems to be increasing in incidence among animals in the United States, especially in the South, where recently Sellers (1941) has reported it to be epizootic among wild foxes. On some of the great cattle ranches in South America the disease is a serious menace.

Symptoms in the Dog—The first sign in the fortunately relatively infrequent 'furious' form of rabies is usually a change in disposition, the animal becoming increasingly restless and snappy. Then a great thirst develops, the attempts to swallow being embarrassed by a progressive paralysis of the pharyngeal muscles, salivation becomes marked and the mouth may 'foam', there is depravity of appetite and a tendency to emit low howls followed by a series of unnatural barks during which the jaws do not close, and the animal starts out on a long excursion without definite destination, usually traveling at a rapid pace and biting many inanimate and animate objects encountered en route. Finally there supervenes the paralytic stage and death. The disease runs its course in from two to eight days. In so-called 'dumb' rabies, drowsiness and paralysis are more marked from the beginning, and death is merely quicker.

Rabies is particularly dangerous in cats for these animals, when infected, often sink into a dark retreat from which they fly out at the passerby, inflicting severe face wounds.

Symptoms in Man—I quote Williams' description: "Furious rabies is the most frequent form in man. For about forty-eight hours there are usually indefinite nervous symptoms, such as a sensation of constriction in the throat, or difficulty in walking or breathing or precordial anxiety, or neuralgic pains. The temperature is slightly increased 100.4° to 102.2° F (38° to 39° C). The fear of water usually develops, due to painful spasm from attempts to swallow. Characteristic reflexes may be caused by a draft of air (aerophobia) or loud noises (hyperacusis). Remissions usually occur except in the very severely infected cases. After about forty-eight hours the excitement increases accompanied by hallucinations and even mania, though usually no attempt is made to injure others. The mind is clear between attacks. The voice becomes hoarse, but there is no real harking. The eyes may show photophobia, nystagmus, strabismus and unequally dilated pupils. Vomiting usually occurs. The patient may die suddenly during this stage after one to four days, but he usually passes into the paralytic stage, with muscles relaxed, jaw dropped, copious saliva flowing and finally into a comatose condition. Death occurs in about two to eighteen hours. Just before death the temperature may reach 107.6° to 111.2° F (42° to 44° C).

'Dumb rabies is less frequent in man than in lower animals. Its recognition is particularly necessary, so that it may be differentiated from the paralysis which very rarely occurs during or just after the Pasteur treatment. The onset may be convulsive, but the lower extremities feel very heavy and numb, then there quickly develops a condition of ataxia and progressive paralysis. Death occurs in from two to eight days from heart paralysis."

THERAPY

Treatment of the Dog—A dog manifesting undoubted symptoms of rabies should be killed at once and his head shipped, either packed in ice or in equal

parts of glycerin and water, in the nearest laboratory equipped to make a confirmatory search for the Negri bodies either directly or after injection into mice by the new technic of Webster and Dawson. All animals definitely known to have been bitten by him should be destroyed if possible, otherwise quarantined in isolation for three months (there has recently been reported from California [J A M A, 115, 1100, 1040] a presumable incubation period of one hundred thirteen days in a dog bitten by a rabid dog). If, however, the dog is only suspected of having the disease he should not be killed but quarantined for observation, for a negative laboratory examination at this time would only leave the diagnosis in doubt. There need be no fear that he will recover from a 'light' case during the period of quarantine for all animals having rabies die. An animal showing no symptoms after three weeks in quarantine is considered not to have the disease, indeed it is the policy of some public health departments to quarantine suspected animals only for seven to ten days since the saliva of a rabid animal does not become infectious until two to five (recently stated as eight) days before clinical symptoms appear.

Local Treatment of the Bitten Human—Until relatively recently there has been little doubt of the paramount importance of thorough cauterization of the wound with fuming nitric acid as soon as possible after the bite has been received. But then there appeared an answer to a query in the Journal of the American Medical Association (112, 1283 [Apr. 1] 1939) to the effect that cleansing with soap and water and subsequent irrigation with saline solution might be the preferable treatment. Since the point is one of quite immense importance a controversial exchange of opinions subsequently appeared in the Journal in which it seemed to me the proponents of cauterization came out the winners. I liked particularly the points made by Kellogg (1940), of the California Department of Public Health which may be tersely stated as follows: (a) The portal of entry of rabies virus is not the lymphatics or blood stream therefore the citing of evidence that particulate matter is carried away rapidly through the lymphatics from the site of its introduction has no validity here, (b) rabies virus travels centrally by way of the nerve trunks only, and very slowly, (c) fuming nitric acid not only destroys tissues and virus on the surface but it also effects some penetration and destruction at an appreciable depth, (d) since vaccination treatment can protect against only a limited amount of virus it is important that as much be destroyed at the site of entry as possible, (e) considerations of scarring should have no weight, for it is just on the face from which the virus can most rapidly reach the central nervous system, that the use of nitric acid cauterization is most imperatively necessary.

Vaccine Treatment of the Bitten Human—The incubation period of the disease in man is between twelve and one hundred days with an average of forty. Hajare (1933), to be sure has recorded a case developing after fourteen months and Isengar (1933) nearly three and one third years the possibility of fresh infection during the interval having been excluded in the opinion of both authors but since such a student of the disease as Webster (1937) of the Rockefeller Institute, has said that one may unquestionably contract rabies merely by intimate contact with a rabid dog without actually being bitten, and since in the first stage of 'furious' rabies a dog may become excessively affectionate instead of vicious there would seem some reason to doubt the validity of these cases (incidentally, Schlotthauer [1938] says upon

what authority I do not know, that whereas fluid saliva may remain infective for more than twenty four hours, dried saliva is noninfective after fourteen hours) It is during this incubation period that the proper use of prophylactic vaccine will prevent the disease in the vast majority of cases, indeed, the failures constitute only 0.26 per cent in arm bitten cases and 1.59 per cent in head bitten cases according to the latest League of Nations Health Section report (McKendrick, 1940) I am aware that there is currently some skepticism regarding the true significance of these figures since the variable factors are necessarily very many Was the dog rabid did he really bite the individual, did he bite through clothing was a potent vaccine used was the individual one of the 73 per cent who would not have developed the disease even without vaccine?, and so forth But until there are forthcoming more significant data to be used against the vaccine than those of Denison and Dowling (1939), whose studies in Alabama have brought the question to the forefront in the United States I feel it the bounden duty of the physician to vaccinate his patient in all instances in which it has traditionally been believed such practice is indicated One may safely wait for the appearance or nonappearance of symptoms in a quarantined dog before starting the treatment unless the bite has been received on the face or hands in which case owing to the short incubation period following wounds at either of these sites, the physician is usually well advised to begin treatment at once—unless of course, he is firmly convinced of the dog's innocence Pregnant and nursing women may be treated with safety

It is no longer necessary to send a patient at great expense to a 'Pasteur institute' for treatment, as any physician can administer the vaccine in the improved form in which it now appears on the market The question of live or attenuated vaccine as employed in the Pasteur method and several of its subsequent modifications versus 'dead' vaccine, as employed in the Semple phenol killed method, was to be settled at an International Rabies Conference to have been held just at the time of the outbreak of World War II However, I think the question is being settled without the Conference for the weight of evidence is in favor of Semple (phenol killed) vaccine upon two counts (a) It is just as effective as Pasteur (attenuated) vaccine, and (b) it is much less likely to cause postvaccinal symptoms There are numerous evidences, however, that commercial vaccines vary greatly in potency, and it is therefore fortunate that Webster (1941) has devised a mouse immunization test by which standardization can now be accomplished Most of the pharmaceutical houses send out the vaccine in syringes containing 0.5 to 2 cc ready for injection when the accompanying sterile needle is attached The contents of a syringe is usually administered daily over a period of fourteen to twenty-eight days according to the severity of the case (*i.e.*, the location and extent of the wound), but it is sometimes advisable to give two injections daily for the first five to seven days—for example, in bites about the face, in severe bites on the upper limbs, in instances in which there has been considerable delay between the bite and institution of treatment, and in children in whom the virus has not far to travel from any point at which it is introduced

The duration of immunity in man after vaccine treatment is probably no more than fourteen months, though to be sure there are very few available data on the subject A person bitten a year or more after taking the Pasteur

treatment should again go through a full course of injections Remlinger and Bailly (1931) have reported an instance of 4 full antirabies treatments in four years a second case of 3 treatments in four years and a third of 2 treatments in seventeen years There were no anaphylactic accidents in any of the cases Kohn Richards (1939) has also kindly informed me that three individuals in his laboratory having completed the Semple vaccine injections in August found it necessary to repeat the course in the succeeding February because of a new exposure Skin tests with the vaccine diluted 1:200 were first performed but being negative the first injections were given One of the individuals experienced syncope headache and vomiting within a minute but this was held to be a psychic reaction In all the succeeding injections in the group 0.1 cc. was first given as a trial dose and the injection was completed after two minutes there were no untoward reactions

I do not believe that the vaccine *per se* is actually responsible for any of the varied symptoms manifested by patients taking the Pasteur treatment In my own case despite the fact that treatment was begun early and that the vaccine was for the most part self administered I was the victim of a certain unwonted apprehension and was thoroughly weary of the irksome routine long before the course was completed In the layman these things might easily make for a quite variegated display of neuroses I found the intramuscular injections into the buttocks distinctly less painful than those placed subcutaneously in the abdomen

Postvaccinal Accidents—Two serious occurrences however do sometimes accompany or follow the treatment they are paralysis and polyneuritis Recovery is the rule though a few persons have died in the paralysis The percentage incidence of these severe symptoms is exceedingly low but it varies so widely in the numerous published reports that it is difficult to state a normal or average expectancy However it is never high enough to be considered a contraindication to the treatment and is certainly much less with killed than with live virus Horack (1939) has presented the interesting hypothesis that these rare reactions are of an allergic nature

Treatment of Rabies in the Human—This can only be directed toward a relief of the suffering as no cure of a proved case has ever been accomplished so far as I know Five per cent cocaine solution may give relief if sprayed well down into the pharynx Indicative of the degree of excitement is the experience of Hart and Evans (1939) whose patient was unable to sleep or rest and had to be shackled to the bed despite the administration of the following medication within a twenty four hour period 12 grains (0.75 Gm.) pentobarbital sodium rectally 10 grains (0.6 Gm.) phenobarbital sodium intramuscularly 60 grains (4 Gm.) chloral hydrate rectally 1 grain (0.06 Gm.) morphine sulfate intramuscularly One of the sulfonamides was tried in this case without effect

Protective Vaccination of Dogs—Winslow (1934) trenchantly pointed out on the basis of most unsatisfactory experience with the attempted enforcement of vaccination in Seattle that the hope of accomplishing much with the standard method of giving 1 subcutaneous injection of a phenol killed virus to dogs is *a priori* absurd since to protect man for a year requires 14 to 28 injections Certainly the subject is still in the experimental stage Leach and Johnson (1940) in apparently carefully performed studies found that such an injection does afford some protection against live virus inoc

ulated from twenty-eight to forty-one days later, but that when the vaccine is given intraperitoneally the protection afforded is considerably less, they also found that chloroform—instead of phenol treated vaccine—was more effective. Kligler and Bernkopf (1941) have recently reported good success in a small series of animals injected with formalized culture vaccines. There are no really reliable figures available on the duration of such protection as may be conferred by any of these vaccines. In a region in Brazil infested with vampire bats, Molina (1938) has stated that cattle given 1 injection annually for three years appear to acquire a solid immunity.

RAT-BITE FEVER

(Sodoku)

This is an infectious disease which follows usually the bite of a wild rat or other animals which have been known to act occasionally as vectors are the cat, pig, dog, monkey, squirrel, ferret, weasel and field mouse. It has long been known and principally studied, in Japan, but authentic cases are being increasingly reported from various other parts of the world. Futaki and Ishiware discovered the causative spirochete, *Spirillum minus* in 1915. After an incubation period of four days to several weeks, the wound site becomes secondarily inflamed and soon ulcerates, there is accompanying regional adenitis, and the patient experiences a paroxysm characterized by gastro intestinal symptoms, fever, and an exanthematous rash. The symptoms last about two days and disappear by crisis, reappearing in a few days however, and continuing a relapsing course for several months. Sodoku is characterized by progressive anemia. The appearance of the organism in the blood of an albino mouse inoculated intraperitoneally with venous blood of the patient affords positive laboratory substantiation of the clinical diagnosis. The Kahn test is apparently usually positive but the Wassermann reaction shows considerable variation. Mortality is about 10 per cent in untreated cases.

It is suggested that the reader also study the article on Haverhill Fever (see Index).

THERAPY

Neoarsphenamine is curative in 5 to 6 injections at intervals of one week, I have seen no record of the employment of mapharsen but see no reason why it should not be equally effective. Acetarsone (stovarsol) has been satisfactorily used by mouth and also bismuth by injection. The doses of these drugs are those used in syphilis.

RELAPSING FEVER

(Spirillum Feter, African Tick Fever)

Relapsing fever is a remarkable disease which is caused by several varieties of a spirochete, *Borrelia recurrentis*, that is transferred to man by insects. The 'European' variety of the disease is not conveyed by the bite of the insect but by crushing into the bite wound or the excoriation made by scratching, or by conveying the infective material to the conjunctivae. Chung and Wei (1939) have shown that the excreta of these insects are not infective. In this variety it is the body and head louse, and perhaps also exceptionally flies, mosquitoes and bedbugs which are the vectors. The disease is endemic in Great Britain, especially Ireland, the Continent including European Russia (it was one of the 'natural forces' which helped to decimate Napoleon's army in the retreat from Moscow), the Balkan States, and the whole of the Mediterranean basin. It has also frequently appeared in epidemic form in the Near and Far East and in Central and South America. Europe suffered considerably from it during and subsequent to World War I and the experience will doubtless be the same during World War II. The 'African' variety, which is conveyed by ticks in biting and also transmitted by them through the eggs to the next generation prevails in many 'native' parts of Africa, it also occurs in Palestine, Persia, Central and South America, Mexico and in the western and southwestern States in our own country. Francis (1939) says that California reported 100 cases in a recent five-year period and that observers in Texas collected 238 cases there during the same period. Morrison and Parsons (1941) say they see about half a dozen patients with relapsing fever in Reno, Nevada each summer and feel that probably other physicians elsewhere in the West have similar experiences. These authors report the interesting case of a parturient woman with the disease whose baby developed it six days after its birth. Occasionally sporadic cases are seen in other States and a few have been recorded in Canada. A number of years ago, Fernan Nunez reported a case in Milwaukee in an individual who had just flown there from Panama. The causative organism was discovered in cases of the European variety by Obermeier, in 1873, of the African variety independently in 1904 by Ross Nabarro and Milne in Uganda and Dutton and Todd in the Congo. Dutton succumbed to the disease in proving its transmission by a tick. It is almost certainly established that the small rodents act as the reservoir for these organisms and that certain spirochetal infections in opossums, porcupines, armadillos, monkeys, jackals, calves and horses are identical with relapsing fever in man.

The symptomatology varies somewhat with localities but there is usually a very sudden onset (after an incubation period between two and ten days), with chilliness, severe headache and pains all over the body, dizziness, gastro-intestinal symptoms, and a high fever. The spleen is almost invariably enlarged, the liver much less often, jaundice is not infrequent especially at the crisis. In a variable proportion of cases there is an erythematous or petechial rash which usually starts on the neck. The symptoms last for from four to ten days, with an average of seven days and then disappear by crisis with a drenching sweat, following which the patient seems to be in quite normal health for about a week, then comes a relapse which is usually somewhat milder than the first attack. In Chung and Chang's (1939) very useful

statistical study of 337 cases in North China, there was an average of 3 to 5 relapses in untreated cases, a higher number than is usually expected, I believe, though in rare instances twice this many have been reported. This disease offers many pitfalls in differential diagnosis, particularly in the tropics where many other possibilities confuse the picture. It is easier to detect the organism in the blood of an inoculated small laboratory animal than in that of the patient. Manson Bahr (1940) says the death rate is usually below 6 per cent but it has been very much higher in some outbreaks. Many complications may occur during convalescence.

THErapy

Most men report enthusiastically upon the use of neoparsphenamine in relapsing fever. Gillespie (1935) said that one dose will suffice in practically all cases if it is properly given. He recommended 0.01 Gm. of neoparsphenamine per kilogram (2.2 pounds) body weight, this single dose to be administered at the onset of a paroxysm, treatment instituted during the middle or terminal stages of a febrile paroxysm, or during the afebrile period, is likely to permit the occurrence of relapses with an increased frequency of complications. In Manson Bahr's (1940) experience a second injection has rarely been necessary, and of Chung and Chang's (1939) 281 treated cases only 16 required a second treatment. I see no reason why mapharsen could not be used with its usual advantages over neoparsphenamine. Morrison and Parsons (1941) gave 0.075 Gm. of sulfarsphenamine, and after thirty-six hours an additional 0.1 Gm., to their six-day old infant (see above). However, some patients do not respond well or even at all to the arsphenamines. Francis (1939) reports three failures in his recent experience and reminds us that others have had similar experiences. Manson Bahr seems to feel that failure is especially likely to occur in African cases—which is the type we have in the United States. Atkey (1939) has given mercury intramuscularly, and Todd (1939) bismuth, both with apparently satisfactory results. In one of Francis' cases he employed convalescent serum (collected seven and one-half months after the donor had been infected with the Texas strain) in the ninth relapse after which the patient recovered.

RHEUMATIC AFFECTIONS

RHEUMATIC FEVER

(NOTE: The reader will probably find it of advantage to study the articles on Acute Myocarditis and Congestive Heart Failure in connection with this present article.)

Rheumatic fever is an acute disease characterized pathologically by the appearance of minute, focal, proliferative lesions in certain tissues of the body, and clinically by fever, pronounced toxemia, proliferative and exudative arthritis, usually proliferative valvulitis (endocarditis), and sometimes pericarditis, pleuritis, and a type of intercurrent pneumonia in which there are transient consolidations and the onset is without chill and often without

involvement occurs in about 70 per cent of cases and many investigators believe that there is some degree of damage in the remaining cases even though it may not be demonstrable at the time. The experience of Boone and Levine (1938), probably according with that of many others, is that the incidence of cardiac damage of recognizable degree is much greater if there is also a history of chorea. The signs of cardiac involvement—development of murmurs, pericardial rub, elevated pulse rate during sleep, conduction changes observable in the electrocardiogram, beginning congestive failure—should be diligently sought, not because there is much that can be done to forestall or limit the involvement during the acute attack, but for the important reason that accurate knowledge of the time of its appearance and the extent of its existence will dictate the management of the convalescence. The exact place of such laboratory diagnostic aids as the sedimentation index, the Weltman reaction, formol gel and fibrinolysin tests has not been determined, I believe. Taussig and Hecht (1938) have seen the beginning of hypertension a number of times during acute rheumatic episodes.

Hedley's (1941) statistical study of 862 cases indicates that the first attack is fatal in 3.5 to 4.5 per cent of instances, the mortality being even higher if cases of rheumatic carditis without arthritic manifestations are included. Martin (1940) reports a total mortality of 30 per cent among 1378 children followed for eighteen years, over half the deaths occurring within five years of the initial attack, findings in agreement with those of numerous other observers. These children usually die from the direct onslaught of the disease and not from congestive heart failure.

When the heart has been only slightly involved the physical signs of this involvement may disappear altogether, but certainly such a thing occurs only occasionally. It is almost a rule that there is increasing injury to the heart as the bouts follow one another, and then long after the rheumatic attacks have ceased to occur, these hearts begin to fail. About one-half to two-thirds (Ritchie, 1936) of those who have suffered from rheumatic fever are cardiac cripples before the age of fifty.

De Baillou (1538-1616), whom Crookshank declared to be "the first epidemiologist of modern times," introduced the term "rheumatism." It was as recent as 1836 that Jean Baptiste Bouillaud established what he called the "*law of coincidence*" between the occurrence of heart disease and this malady.

THERAPY

Nursing Care—The patient's comfort can be much increased by transferring him to a blanketed bed and wrapping the affected joints in many layers of cotton. He should be carefully protected from the chilling to which he is liable by reason of the sweating, i.e., if he is not under a cradle and cannot bear the weight of sufficient covering to protect the body from excessive evaporation from its surface, then ventilation in the room must be restricted accordingly. In so far as is possible the gown and bedclothes should be changed as soon as they become wet, but judgment must be exercised here for at times such manipulations will be little short of cruel.

The patient should be kept in bed for a month after disappearance of symptoms in even the lightest cases. Struther's (1940) recommendation seems

and biologicals that are used in other diseases, the salicylates do not shorten the duration of an attack of rheumatic fever, nor do they lessen the incidence of valvulitis, etc., but there are reports (Boas and Ellenberg 1940, and others) of the successful salicylate treatment of rheumatic pericarditis with effusion (2) Careful research has failed to show the salicylates responsible for antibody increase (3) Salicylic acid is bactericidal in the test tube, but it is extremely improbable that it can accumulate in the tissues in sufficient quantity, under the conditions existing in the living body, to be bactericidal there during life (4) The salicylates seem specifically to stimulate the excretion of uric acid while not affecting quantitatively to any marked degree the other common constituents of urine This stimulation, though independent of the volume of the urine, does not begin until the drug reaches a certain concentration in the organism and ceases promptly when concentration falls below this level The significance of these observations (Quick, 1933) in relation to rheumatic fever is unknown, but it is noteworthy that the effect on uric acid excretion begins at a lower concentration of the drug than is necessary to bring about relief in rheumatic fever

The synthetics are fully as good as the natural products as was amply shown by the independent laboratory and clinical studies of Waddell and Hewlett Not a whit more toxic either—and the naturals' are several hundred per cent more expensive (A tale not often told I think has been recited by Wilkinson [1935] MacLagan thought that acute rheumatism was allied to malaria, i.e., that it was a miasmatic disease, liable to appear in low lying damp localities at certain seasons And since a beneficent providence had supplied a cure for malaria in the bark of a tree indigenous where malaria was endemic, the remedy for rheumatism was to be sought in the bark of a tree which grew in damp, low lying sites He hunted, found salicin in the bark of a willow, published the discovery in 1876, and within three years the salicylates were in general use wherever acute rheumatism was prevalent A bit apocryphal, perhaps, since the ancients knew the antipyretic properties of willow bark and, according to Goodman and Gilman [1941] salicin had been discovered by Leroux in 1827, but still a good story!)

Sodium Salicylate—This is perhaps the most used preparation The ideal system is to give the drug every hour for 8 or 10 doses then stop for twelve or twenty four hours, depending upon the gravity of the case, upon resuming the same dose should be given every four hours until a week or ten days after the disappearance of all symptoms when it may be discontinued by a gradual diminution of the dose In perhaps the majority of cases the patient will not tolerate as much as 8 hourly doses, in which event the drug should be given at this time interval only until the first signs of saturation appear (tinnitus deafness, slight visual disturbances nausea, vomiting and perhaps diarrhoea) Dosage attempt to give 20 grains (1.3 Gm.) to all individuals of twenty years and over, reduce 1 grain (0.06 Gm.) for each year under twenty This is of course top dosage Taussig (1935) says that at the Harriet Lane Home of the Johns Hopkins Hospital she is not often obliged to give children more than 45 grains (3 Gm.) of salicylates daily

The gastric irritation manifested by nearly all patients can be lessened by prescribing the same or preferably double the amount of sodium or potassium bicarbonate with the salicylate A few physicians use capsules or powders, but for most adults—necessarily for children—solutions are pref

erable Wilkinson adopts the very practical measure of giving 2 prescriptions with different flavoring for alternate use, and then changes the flavorings completely every few days I suggest the following basic prescription

R. Sodium salicylate	℥iiss	10 0
Potassium bicarbonate	℥v	20 0
Aqueous elixir glycyrrhiza	℥ij	60 0
Syrup glycyrrhiza to make	℥iv	120 0

Label One or more teaspoonfuls in water as directed. (Note each teaspoonful contains 5 grains (0.3 Gm.) salicylate and twice as much bicarbonate.)

Leaving all quantities unchanged, this may be entirely altered in flavor by making any one of the following substitutions for the aqueous elixir and syrup of glycyrrhiza (I am employing vehicles usually liked by children)

Cinnamon water	Water
Syrup cinnamon	Syrup raspberry
Spearmint water	Compound elixir vanilla
Syrup glycyrrhiza	Syrup tolu
	Water
	Syrup cacao

Any of these mixtures is likely to become discolored and develop a dark precipitate upon standing

When gastric irritation limits the dosage to less than is necessary to obtain the therapeutic effect, the drug may be given by rectum Heyn has reported a series of 125 cases satisfactorily treated in this way His technique follows

"A cleansing soap-suds enema is given [I believe 1 per cent sodium bicarbonate would be better] and as soon as effective is followed by the salicylate enema given by means of a Davidson syringe and a rectal tube inserted 6 to 8 inches The dose varies according to the size and sex of the patient and also according to the severity of the case The first adult dose in men is usually 8 to 10 Gm [120 to 150 grains], in women 6 Gm [90 grains], women being apparently more susceptible to salicylism than men The amount of salicylate to be given is incorporated in 120 to 180 cc. of plain or starch water with the addition of 1.0 to 1.5 Gm [15 to 23 minims] of the tincture of opium The dose of salicylate may be repeated in twelve hours, when it can usually be determined whether symptoms of salicylism will appear Usually, however, a daily enema suffices with doses increasing perhaps from 30 to 50 per cent daily until the limit of tolerance is reached The largest daily dose which has been given has been 24 Gm [360 grains] and the only symptoms of salicylism which have usually appeared have been tinnitus and excessive perspiration Once or twice there has been vomiting present, which might occur in the administration of even a simple coema. Where salicylism has been excessive, it usually appears within from three to six hours and the remaining unabsorbed portion of salicylate may be washed out of the bowel by subsequent enema. This has been resorted to very infrequently indeed, and it is rare also that the rectum is intolerant of the drug'

It is doubtful whether intravenous salicylate medication possesses any advantages over the administration of the drug by mouth or rectum, how-

ever, when neither the stomach nor rectum is sufficiently tolerant, it must be resorted to. Mendel, quoted by Fantus, gives the following formula

R Sodium salicylate	8.0 Gm
Caffeine sodium salicylate	2.5 Gm
Sterilized water to make	50.0 cc

Inject 2 Gm (one fourth of this solution) every twelve hours, but be careful. I do not myself approve of giving caffeine intravenously.

Strontium Salicylate—In a patient whose stomach is revolting against sodium salicylate, equivalent doses of strontium salicylate may sometimes be substituted with advantage, but the superiority claimed for the salt some years ago was never proved.

Acetylsalicylic Acid (Aspirin)—This drug is probably more analgesic than sodium salicylate but unless guarded fully with bicarbonate it may easily induce acidosis, and it should certainly be withheld from individuals with a history of gastritis or suggestive of gastric or duodenal ulcer, indeed, Douthwaite and Lintott's (1938) gastrascopic studies showed that aspirin causes inflammatory gastric changes exceedingly frequently. The drug also occasionally gives rise to serious allergic reactions, with several recorded deaths in individuals who were asthmatics. A few years ago Caca *et al* and Prickman and Buchstein stated that aspirin hypersensitivity is the most frequently encountered form of drug allergy, but I think Gardner and Blanton (1940) have done well to point out that the apprehension in the profession subsequent to this statement is perhaps unwarranted since the number of individuals reacting violently to this drug must surely be very small in proportion to those who take it—they found that the amount sold in the United States in the year of which they had record was 5,143,672 pounds!

Aspirin is used in the same doses and at the same intervals as sodium salicylate. It is too insoluble and unstable to be prescribed in water. Assertions have been made, however, that it may be dispensed in water by the aid of sodium citrate and that the acetylsalicylic acid is not decomposed in such a solution. Leech has shown that this is not true, decomposition does take place, and after several days the ingredients of such a solution are just the same as if sodium acetate and sodium salicylate had been used in the first place.

It was formerly held that the use of aspirin and bicarbonates together might increase instead of decrease gastric irritation, but experience has overthrown the contention. A few people experience tachycardia and possibly slight exhalation upon taking aspirin, but the drug is not a heart depressant under the conditions in which it is used in rheumatic fever.

Calcium Acetylsalicylic Acid—The use of this drug to replace aspirin has been urged though it would seem that its greater instability might lead to more and not less gastric irritation than the older drug, however, Douthwaite and Lintott (see above) found it less irritating, probably because of its greater solubility.

Methyl Salicylate (Oil of Wintergreen, Oil of Gaultheria)—This drug is sometimes given in about the same doses as sodium salicylate, dropping it into capsules just before use, but as it is no more efficient than the sodium salt and much more poisonous it should be used, if at all, only to paint on the joints after mixing it with 1 or 2 parts of olive oil.

Salicylates in Prophylaxis—Leech (1930) gave 20 grains (1.3 Gm) of acetylsalicylic acid daily for six months to 67 children with potential heart disease and inactive rheumatic heart disease, controlling the series with 79 similar children untreated. The daily salicylate ration seemed to be the factor which enabled a number of children to gain weight, and presumably an increase in general resistance, but the study was inconclusive with regard to protection against cardiac complications. Perry's (1933) findings, in England, were also of an indefinite nature. Kaiser (1936) used daily doses of 10 to 15 grains (0.6 to 1 Gm) of acetylsalicylic acid, supplemented by an equal quantity of magnesium oxide to "potentiate" the antirheumatic drug and felt that in comparing untreated and treated groups, each of 75 children with similar manifestations, there were fewer major recurrent attacks among the treated. No benefit was noted in those who had evidence of rheumatic carditis alone. The most recent report I have seen is that of Schlesinger (1938), who has had much experience with rheumatic fever in England and has become so enthusiastic about the routine administration of aspirin in every case of throat infection in rheumatic children that he recommends its adoption by all physicians. The drug must be given immediately upon onset of the sore throat and continued daily for four weeks, the thrice daily dose is from five to eight years 7 grains (0.5 Gm), nine to fourteen years 10 grains (0.6 Gm), above fourteen years 10 to 12 grains (0.6 to 0.75 Gm). He says that relapses have become much more rare since the adoption of this regimen (which had been in effect at the Children's Heart Hospital for seven years at the time of his report) and that when an attack of rheumatism or carditis does occur it is much milder than formerly.

The Cinchophens—In view of the very serious type of poisoning which these drugs occasionally induce and since we can accomplish nothing with them that is not equally possible with the salicylates, I believe I am justified in taking the position here that their use in the treatment of rheumatic fever should be abandoned.

Amidopyrine (Pyramidon)—This drug is usually fully as effective as the salicylates in reducing symptoms but like them does not influence the incidence of complications or the tendency toward relapse. It is much used in place of the salicylates on the Continent. Schultz (1931) pointed out the advantage lying in the absence of gastric irritation under this drug which permits certain identification of epigastric discomfort and tenderness, nausea and loss of appetite as the visceral congestive signs of cardiac insufficiency. Heninger and McHardy (1938) gave 10 grains (0.6 Gm) thrice daily to individuals of any age but Taussig (1935) had earlier shown that such dosage is not necessary, at least in children, she gives 20 grains (1.3 Gm) as maximum total for the first twenty-four hours and usually reduces this on the second day to 15 grains (1.0 Gm) as maintenance dosage.

Warning! The very serious clinical entity agranulocytosis (see Index) has been shown many times to be caused by the use of this drug.

Sulfonamides in Treatment—The studies of Swift *et al* (1938), and of Massell and Jones (1938), have shown that not only are these drugs of no therapeutic value in rheumatic fever but in addition that their use actually aggravates the severity of an attack. They therefore seem to be definitely contraindicated.

Miscellaneous Measures—*Nitranol*—There is no doubt that this drug

which is used in chorea has a definite antirheumatic effect in some patients but it fails in many instances and I see no reason for ever preferring it to the salicylates *Sulfur and Iodine*—In Germany various proprietary combinations of these two drugs have been employed by a few clinicians but I have not as yet found a carefully controlled study of their effectiveness *Anti-streptococcus Preparations*—Both in this country and in England small groups (Swift *et al* Small Collis and Sheldon Wasson and Brown) have been studying the effect of serums and vaccines variously prepared in their laboratories and believe that they have at times been able to induce a state of resistance in their patients. Of course satisfactory evidence of this sort would be very difficult to adduce many physicians believe that the whole attempt has no rationale since we do not know with certainty whether the streptococcus is the etiologic agent in rheumatic fever. The preparations are not commercially available *Fever Therapy*—The earlier attempts to induce whatever nonspecific effect may be obtained by injections of milk or typhoid vaccines have now given way to the employment of the hyperthermia cabinet. The latest significant study I have seen is that of Simmons and Dunn (1939) who have been employing the method for some years. Prompt and complete relief of joint pains and swelling were obtained in nearly all the cases in which these symptoms were prominent, and there was no evidence that the severity of cardiac involvement was increased. But the group studied comprised only 31 patients and these authors certainly express the consensus in saying that more time must elapse and much larger groups be observed before the position of fever therapy can be established *X-ray Therapy*—Upon the basis of eleven years' experience in 48 patients Levy and Golden (1937) felt that irradiation of the heart deserved a place in the therapy of properly selected cases of active carditis but of course an experience much greater than this would be required to prove the point in a disease so variable as rheumatic fever *Convalescent Serum*—Friedman *et al* (1938) saw no evidence of benefit from the use of this agent in 4 patients during an acute attack *Treatment of the Anemia*—Because of the associated anemia it is usually profitable to attempt to build up the blood picture for methods see the section on The Anemias *Change of Climate*—Since we have no definite knowledge of the influences underlying the geographical distribution of rheumatic fever it would seem that one should be very hesitant about recommending a radical change of climate. In our country nevertheless it is not unusual for the parents of a rheumatic child to be advised to move the family permanently to a warm climate but southern California, Arizona and southern Florida appear to be about equally favored in such advice though these are radically different types of climate. A report before the American Rheumatism Association (JAMA Oct 16 1937) a few years ago indicated that a shift to Florida at least is not a panacea. Tappan (1939) herself of Arizona has said that unless children of the underprivileged classes are kept out of the crowded conditions of cheap tourist accommodations when transported into a new climate and unless they can have necessary hospital and convalescent care in the new location they are better kept at home. She says further there are no accurate means of gauging whether an active rheumatic infection clears more rapidly in Arizona. Obviously this whole subject needs to be studied a great deal still.

Sulfonamides in Prophylaxis—Coburn and Moore (1939) gave sulfon

amides to rheumatic children after the onset of streptococcic pharyngeal infections and failed to prevent rheumatic recrudescences, but 79 of the 80 rheumatic children given the drugs continuously throughout the winter escaped hemolytic streptococcic infection and signs of recurring rheumatic activity as well. From the nature of their studies adequate controls were not possible, however, in the entire series. But the study of Thomas *et al* (1941), in which the controls were about as adequate as is possible in work of this nature, do seem to offer very strong evidence of the value of sulfonamides in the prevention of rheumatic recrudescences. Their study continued through four years and in general the patients were started on the drug during October and given it continuously until some time in June. The dose in the beginning of the study was 15 grains (1 Gm) daily, divided into three doses, later this was changed to 20 grains (1.2 Gm) daily, taken in two doses twelve hours apart. There were 55 treated patients observed during seventy nine "person seasons" and 67 untreated patients observed during one hundred and fifty person seasons. While taking the drug none of the treated patients had an acute hemolytic streptococcus infection or a major attack of acute rheumatic fever and there were no deaths in the group but one patient had an attack in August when he was not taking the drug. In the control group there were fifteen major rheumatic attacks (one death), one hemolytic streptococcus infection, two cases of subacute bacterial endocarditis (two deaths), five patients whose illness "might have been of rheumatic character," and one patient died from a cause unknown.

There is, however, a reverse to this coin, for Stowell and Button have reported at the close of 1941 that during the first year of their trials one-half the patients had to give up using the drug because of some toxic reaction. In the second year when the drug had been used but two months, 9 patients out of 82 had to discontinue using it, and 1 death occurred which was attributable to sulfanilamide. Coburn and Moore (1941), stopping the drug in 100 patients after three years of continuous administration found that these individuals developed hemolytic streptococcic pharyngitis and rheumatic fever at about the same rate as their other clinic patients. Stowell and Button have stopped their study and feel that in the present state of our knowledge sulfanilamide should not be used prophylactically in ambulatory rheumatic children and adolescents.

Effect of Tonsillectomy—Here is a tremendously important question, which, so far as I am aware, has not yet been fully answered. Kaiser's (1927-1936) investigations convinced him that the routine procedure of removal was justified in practically every rheumatic child, but in his more recent publication (1940) he does not seem to be so sure on the point. Allan and Baylor (1933) felt that since carditis developed in only six of their forty nine rheumatic patients not having such involvement at the time of operation, tonsillectomy is to be recommended. Leathart (1933) felt it to be urgently indicated in a patient not responding to other treatment. Upon the other hand, the studies of Wilson, Lingg and Croxford (1928) yielded no evidence in favor of the operation and even showed that the incidence of sore throat was not lessened by it. And Ash (1933), studying the effect of the operation upon the course of the disease in 522 rheumatic children, felt that it is indicated only as a remedial measure for definite disease in the tonsils themselves and to be performed only during an inactive phase of the rheumatic affection.

Schlesinger (1938) advises a routine course of aspirin—as used in prophylaxis* (see above) after tonsillectomy. Very few physicians are willing to deny that serious and even fatal flare ups in quiescent cases are sometimes suspiciously associated with tonsillectomy. I think that the following is the consensus of unprejudiced students of this matter. Until someone produces incontrovertible evidence that children without tonsils are definitely protected against rheumatism, routine tonsillectomy is not justified, but when the tonsils are large ragged and septic (but not merely enlarged), or small and accompanied by enlarged glands, the removal of tonsils and adenoids is probably well worth while. Spencer (1934), like many other observers counsels against removal of tonsils in children under four years of age unless there is definite reason for the operation. His partial list of indications is the following: (a) Impaired hearing made worse by each attack of tonsillitis, (b) infected tonsils in patients with goiter, (c) sinus disease though he recognizes that in some instances tonsillectomy may be contraindicated, (d) chronic suppurative otitis media when aggravated by infection of the tonsils, (e) bronchiectasis aggravated by tonsillitis, (f) chorea before it has become chronic.

RHEUMATOID ARTHRITIS

(Chronic Infectious Arthritis, Proliferative Arthritis, Atrophic Arthritis, Arthritis Deformans)

This is the type of arthritis which is seen in individuals in the twenties, thirties and forties more often than at any other age, beginning usually with a gradual involvement of the fingers and wrists. There are local inflammatory and proliferative changes involving primarily the synovial membrane and soft parts of the joints, great pain and tenderness and limitation of motion, migration from joint to joint, and enough new growth of fibrous tissue about the joints to cause persistent periarticular swelling. The skin over the involved areas becomes smooth and shiny, the extremities cold and clammy, and a peculiar selective muscular atrophy takes place. In many instances the attack is preceded by anorexia, easy fatigability, weight loss, vasomotor disturbances, and other evidences of constitutional involvement, during the attack there is often a low grade fever and nearly always an increased sedimentation rate, the latter usually proportional in degree to the severity of the involvement. Ankylosis which is very common in this type of arthritis usually does not appear until after the patient has suffered several attacks. Rheumatic nodules appear frequently, especially in the elbow region. The form of the malady earlier known as arthritis deformans or atrophic arthritis in which there is thickening of the capsule and marked destruction of the articulating surfaces with telescoping of the joints and ulnar deviation of the hands and fingers is now included as merely a very severe grade of rheumatoid arthritis. In a book of this scope it must suffice to consider the following relatively rare maladies as merely unusual forms of rheumatoid arthritis: Still's disease, chronic infectious spondylitis, Marie-Strümpell syndrome, Felty's syndrome, von Bechterew syndrome. The recurring joint disease without articular residues, recently discussed by Hench before the American Rheumatism Association, as well as other types of intermittent arthritis difficult of classification must also be placed here.

It would seem that this is an infectious disease, with most of the evidence tending to incriminate some form of streptococcus, but as yet no specific bacteriologic agent has been conclusively indicated in the etiologic role. Like rheumatic fever, rheumatoid arthritis is encountered only in a 'spotty' distribution in the warmer climates and the incidence is higher among the poor than among the well-to-do, there are other apparent resemblances between the two diseases, but the real nature of the relationship, if there be any, has not been demonstrated. The careful study of Cobb *et al* (1939) caused them to feel that grief and family worry, in addition to poverty, bear more than a chance relationship to the onset and exacerbations of the disease. Evidences of an hereditary factor and of a predisposition to develop rheumatoid arthritis seem to be increasing as our knowledge grows. Differences in racial susceptibility are not pronounced though somewhat fewer Negroes are affected than whites. There is still much confusion among students of this malady. Some point to the frequency of constipation and the low gastric acidity of many of these patients and consider that these things are of at least great contributory importance, decreased functional capacity of the liver is also alleged to be a frequent occurrence. Others cite hypothetical metabolic derangements affecting carbohydrates, proteins, calcium, sulfur, etc. Vitamin deficiencies have been suggested, and the possible allergic or endocrinopathic nature of the malady has not been overlooked. To date, however, the importance of none of these things has been proved. Perhaps the belief that has had the largest number of adherents in recent times is that the disease is initiated from some primary focus of infection in the teeth, tonsils, sinuses, gallbladder, cervix, prostate, colon, or elsewhere—but this viewpoint has been so often challenged, and of late so openly deserted by many of its former adherents, that I think it nowadays no longer holds the forefront of attention. Rheumatoid arthritis does not often directly kill, but it maims and impoverishes and lays a heavy toll upon its victim's fortitude and upon the purse of his community. Recently, Baggenstoss and Rosenberg (1941) at the Mayo Clinic, have demonstrated cardiac lesions in a surprising proportion of necropsies, but much time must pass and further studies be performed before the significance of this finding can be determined for it is contrary to most clinical experience.

Sydenham, in 1683 differentiated rheumatic fever, gout, and chronic rheumatism, but the first sharp delineation of the essential pathology of rheumatoid arthritis was that of Nichols and Richardson, in 1909.

THERAPY

Rest.—It is certainly the consensus among those who have had the largest experience that rest is the most important single item in treatment. Patients know this too and those who must remain ambulant as long as possible always seek to avoid fatigue since they early learn that it invariably aggravates their symptoms. A complete rest cure of six months to a year is the ideal thing and one which has undoubtedly greatly benefited many patients, perhaps even permanently cured a goodly number. But unless the rest can comprise mental as well as physical repose, both often best accomplished away from home, the compromise must be made of persuading the patient who remains active to be down for an hour or two in the middle of the day and to retire to rest if not to sleep very early each evening.

Relief of Pain—It is a rare case in which the salicylates are not used if bedridden, much as in rheumatic fever, if ambulatory, of course in greatly reduced dosage. Unfortunately the relief afforded is often very slight. However, many arthritics take very large doses of aspirin over many years and claim that without it their lives would be unbearable. It is my feeling that here, as in rheumatic fever (*qv*), the cinchophens should not be used. Obviously morphine or dilaudid should not be used, indeed, Ryneerson and Hench pointed out a number of years ago that in conditions diagnosed as rheumatic in which it is necessary to use morphine one had best reconsider the diagnosis. Sometimes, when pain is preventing sleep, 1 grain (0.06 Gm.) of codeine sulfate in combination with a hypnotic will satisfactorily control the situation. Physical therapeutic measures have a considerable though often temporary analgesic effect.

"Building-up" Therapy—Most rheumatoid arthritics are of the lean and scrawny type, many of them are grossly underweight and hypochromic anemia of some degree is practically a constant finding. Certainly it is rational practice to try to 'build up' such people and would be even though they did not have arthritis. But we have as yet no magic wands that are worth the waving. All the present pother about vitamin stuffing is still just pother. What is needed is a good nutritious diet and an attempt to correct the anemia. The latter is not usually easily accomplished with either iron or the liver preparations, unfortunately. Transfusions seem to be many times helpful in the early active cases, Thompson *et al* (1938) also found them sometimes helpful in patients particularly resistant to treatment and whose arthritis is progressive, or in those markedly debilitated with a persistent severe secondary anemia. Bowen and Lockies (1936) study indicated that the use of a high carbohydrate diet plus insulin to increase the appetite, as in the handling of malnutrition *per se*, is not harmful and may even have positive value.

Orthopedic Treatment—As in poliomyelitis so in arthritis the orthopedist is showing the way nowadays. Therefore, before discussing the various types of physical therapy which may be utilized in handling a case it has seemed to me important that the orthopedic approach be mentioned, for the essence of successful orthopedic practice is prevention, not correction of deformity, and when can prevention best begin if not as soon as diagnosis is made? Therefore, it would seem the part of wisdom to have the advice of an orthopedist very early in every fulminating attack. Hench and Meyerding (1934), Swaim (1936), Holbrook and Hill (1936), Stump (1940), and Krusen (1940) are among the leaders who are describing these things in terms understandable to the nonspecialist. (a) The layman's and frequently the physician's belief that to 'keep going' at all costs is the thing indicated to keep the joints supple is quite the reverse of what is practiced in other inflammatory conditions, in which physiologic rest is always enjoined, therefore it is wrong, and what is truly indicated is to immobilize these joints, even with plaster casts if necessary, during the acute stage. Thus muscular spasm for the protection of a sore joint, with the resultant flexion deformity, is prevented. Complete relaxation and total body rest will take place, too, when the patient knows that his every movement will not be painful. (b) The use of a firm bed must be insisted upon even though this firmness can be obtained only by placing a 1 inch board directly beneath a 'hard' mat.

stress, for only thus can gross deformities be avoided in severe cases (c) Fibrous adhesions apparently need not be feared if the cast is split in two days and daily passive motion is instituted and further fixation is continued or not, as the daily expert observation dictates. Even after the joints are entirely freed from splints during the day, the latter should be used to make full rest and sleep possible at night (d) When to start massage and exercises and how much exercise can be given? 'During the acute phase, if an over-zealous physician or even a brave patient fearful of impending deformities, should attempt to start motion prematurely, nature's warning of severe pain and increased spasm generally prevents. The patient holds the joint as still as possible, and nature begs for help in making that rest absolute. But soon the patient will involuntarily at first then under encouragement warily move the joint a little. That is the signal for institution of light massage and very gentle, passive motion. As the subacute stage fades into the chronic stage, pain and tenderness further subside, and active and passive motions are increased. The rules of exercise are relatively simple. Any exercise that does not produce pain either during its administration or afterward is harmless and can be persisted in as long as it remains painless. Any exercise that hurts the joint slightly while it is being carried out, but produces no appreciable 'hang-over,' and is not followed by a significant increase of pain is safe. However, exercise should be avoided which, whether it produces immediate pain or not, is followed by a hang over, such as an increase of pain that day or the next.' The reasons for massage are that it is hoped through it to improve the circulation in the joints and neighboring parts and to preserve muscle tone. Naturally, not just any 'rubbing' will accomplish these things, nor is any one professional masseur as good as another, some of them are much too enthusiastic and do more harm than good in the beginning. The best procedure is to have the work started by a technician who has been properly trained by an orthopedist, and then after a while have some member of the family attempt to take over this work if she can develop the knack (e) The correction of deformity in the quiescent stages of the disease by manipulation and mechanical stretching by manipulation under general anesthesia or by open operation, are measures in which orthopedic surgeons have made great strides in recent times but of course the indications or procedures cannot be described here. The correction of faulty posture is also a matter calling for expert orthopedic advice.

Physical Therapy—Because it seems to me that massage and proper exercises should be at least begun by the orthopedist, I have discussed those measures briefly above, and therefore there remain in this present category only the various methods of applying heat. The objects of heat applications are to allay pain (how this is accomplished we do not know, occasionally the pain is increased instead), to promote circulatory improvement through the induction of hyperemia, and to cause the patient to sweat (we do not know why this is helpful either). The ancients seem to have been busily bathing in thermal springs at the dawn of history and we do well to continue the practice. In many modern hospitals there are all sorts of gadgets for generating heat within the body by means of nodal galvanism, faradism, diathermy and so on but I think we can leave such appliances to the physiotherapists in these institutions hoping that they know as much about them as they appear to do. Any physician wishing to

learn the location of the nearest registered technician in physical and occupational therapy has but to make enquiry of the following agencies: American Registry of Physical Therapy Technicians, 30 N. Michigan Ave., Chicago; American Physiotherapy Association, 737 N. Michigan Ave., Chicago; American Occupational Therapy Association, 175 Fifth Ave., New York. In these pages I shall merely outline the methods for applying heat in the home without the benefit of specially trained assistants.

The Complete Bath—The patient gets into the bath with its temperature at about 100°F (38°C) and during fifteen minutes the temperature is raised to about 104°F (40°C), he stays in the bath for a total of thirty to forty five minutes and then goes to bed and continues his sweat under plenty of cover. The bath should be begun with the stomach empty but after it is over light food may be taken, while in the tub a cold wet towel should be kept wrapped around the head to prevent headache and faintness. Such baths should not be given to patients with arteriosclerosis, any sort of cardiac abnormality, or organic nervous disease and they should be employed with extreme caution in asthenic or debilitated individuals.

Six pounds of ordinary salt added to the bathtubful of water (50 to 60 gallons) will give a salt content equivalent to that of the sea. Such a brine bath retains heat longer and probably stimulates perspiration better than plain water, its buoyancy is of assistance also if active movements are to be performed. The mustard bath ($\frac{1}{2}$ ounce of mustard per gallon of water mixed first with a little cold water) is somewhat too irritating for most skins.

The complete bath would seem to be the simplest way of applying fever therapy, the temperature rising considerably due to temporary abolition of surface radiation.

The Partial Bath—All of the local effects of hot bathing can be obtained by simply immersing the affected joints such as fingers, wrists, ankles, etc., in a suitable receptacle. For a hip bath the patient may sit in an ordinary clothes washing tub with the feet and arms outside, if the feet are then placed in another tub or bucket of hot water and the whole ensemble except the head is covered by a blanket, he is taking the famous "sitz bath" (of course this can be accomplished by having him sit in a partially filled bathtub with knees up and only hips and lower legs and feet in the water, but the modern tub against the wall is difficult to drape). The temperature of such partial immersion baths may be safely brought up to 110°F (43.3°C), but it should be remembered that general sweating of the body is likely to be induced and the patient should be protected against its excessive evaporation and the consequent chilling.

Contrast Baths—In rare instances the patient seems to profit by the alternate application of heat and cold. This can of course be simply accomplished by placing the extremity in hot water, then cold water, then hot water, etc., but one must always begin and end with heat.

The Paraffin "Bath"—A sufficient number of cakes of paraffin (procureable at any grocery) is melted in a receptacle of the proper size and shape to admit the hand or foot, and then, just when a thin film has begun to form on the surface of the paraffin, the member is plunged in, held in the hot paraffin for ten to thirty seconds, removed and, after the coating has dried in thirty to sixty seconds, returned to the paraffin bath. This is repeated until six or eight coats have been applied. The member is then placed at rest on a cushion.

and covered with a blanket. The paraffin is easily removable—it is usually retained in place for thirty to sixty minutes—because much perspiration gathers beneath it.

A modification of the above method is to paint many coatings of paraffin over the joint with an ordinary paint brush or a swab on a stick. Krusen (1940) speaks favorably, too, of applying alternate layers of gauze and paraffin which may then be left on as a comfortable support until the treatment is repeated next day. It is best either to shave or oil a hairy region before applying paraffin.

Packs.—Mustard Make a paste by stirring a teaspoonful of mustard into tepid water, then stir this into a pint of nearly boiling water. A towel wrung out of this hot mustard water is applied to the part, covered with a blanket and left in place for five to ten minutes. Afterward sponge away all the remnants of mustard with warm water and under no circumstances apply this pack at all if the skin is broken. **Mud** Add powdered fullers' earth (kaolin) to a receptacle of nearly boiling water until this acquires poultice consistency, having previously placed close at hand a piece of linen or cotton cloth covered with a layer of gauze. Quickly transfer the mass to the cloth in a layer about 1 inch thick, mold it about the affected part, cover with a blanket, and leave in place about thirty minutes.

Radiant Heat—In the hospitals there are electric light cabinets and infra red lamps which are very effectively used. Ray (1936), whose excellent series of articles much assisted me in the original preparation of this outline, described a simple home substitute provided by making two bricks red hot in a fire and placing them at the bottom of an old bucket. "Over this a limb may be supported, covered by blankets, a knee, elbow, wrist, ankle, foot, or hand can thus be exposed to infra red rays which are just as efficacious as those derived from a more expensive electrical apparatus." Krusen's (1940) inexpensive homemade heater may be constructed of a piece of ordinary sheet tin curved in a roof like fashion on a framework of strap iron or rods. Two double electric sockets are attached to the under surface of the roof and the necessary wiring is installed. Bulbs of 60 or 120 watts may be used to obtain the desired amount of heat.

Climatic and Spa Treatment—There comes a time in the course of most cases of arthritis when the patient will be benefited psychically if not otherwise, by a trip to a spa, but unfortunately the economic strain of such a sojourn cannot be borne by the majority of individuals. Likewise, those who can move permanently into a warm climate, not necessarily dry, may be benefited if the malady is not too far advanced, but see *Change of Climate* in Rheumatic Fever.

Employment—Some years ago Coulter pointed out that occupational therapy can be applied at home if the patient, physician and family will earnestly set about finding tasks which will provide opportunity for the repetition of exact motions—for example, for bending and straightening the leg at work while the patient is thinking about his job, he suggests refinishing wooden furniture, which involves constant squatting and rising as the rungs and other parts of a chair are worked upon. How to return each crippled individual to a job in which he can regain economic freedom at a cost to his self respect that is not excessive is a problem indeed, but the physician must help bear the burden of trying to solve it.

Eradication of Foci of Infection—This is by no means a strictly modern approach, for according to Osgood (1940) we find the physician to Ashurbanipal, King of Assyria in the seventh century before Christ, advising his master as follows "He will speak the truth with the king as the king demanded the pain in his head, his sides and his feet has come from his teeth, they must be extracted." Nowadays even if a physician knows little else about the disease, he is sure to know that "eradication of focal infection is absolutely indicated. But why—if this indication is so absolute and in consideration of the almost routine fashion in which it is met—do we not see more uniformly good results? Occasionally, to be sure, the response is startling and there is a case to report and moralize upon but it does not happen with any great frequency and sometimes an exacerbation is unquestionably initiated. Solis Cohen (1934) opined that in "eradicating" a focus we do not get rid of the bacteria anyway, for they continue to live and multiply in the tissues surrounding the area from which the "focus" was removed, perhaps he is right. Even many of the enthusiastic advocates of this type of treatment are now admitting its futility in cases that are far advanced and some of the leading students of arthritis seem to be changing their minds. In 1933, Cecil wrote "the keystone of the modern treatment of rheumatoid arthritis is the elimination of infected foci." In 1938 he and Angevine were saying "the time has arrived for a complete revaluation of the focal infection theory." Finally, in a Cornell Conference on Therapy, in 1941, he has said "In respect to rheumatoid arthritis the theory of focal infection is generally discredited because students of arthritis have found first, that in a great many patients the disease develops without any association with foci and, second that those who have had foci of infection removed have obtained only temporary benefit, if any at all. The disease goes on its progressive course, even after tonsils, teeth, and other suspected organs have been removed." Reimann and Havens (1940) in a critical appraisal of the entire subject of focal infection and systemic disease, were unable to make out a case in favor either of the theory or of the routine "eradications" based upon it.

Miscellaneous Measures—Some years ago Miller (1936) performed a fine service by reemphasizing that (a) rheumatoid arthritis is characterized by a variable onset and a course in which remissions are not uncommon, (b) *therefore any claims for the effectiveness of a remedial measure can be valid only if the measure was applied in a study employing the control method and then only if the improvement consistently sets in shortly after the treatment is started. With these things in mind the following measures do not seem to warrant description as major items.*

Fever Therapy—Apparently such relief as is afforded by fever therapy occurs in a very variable proportion of cases and is only temporary in practically all instances. I know of no one in an authoritative position in this field who is now recommending fever therapy as the method of choice.

Vaccines—A few sanguine individuals are still hopeful of establishing the value of vaccine therapy in arthritis, one can only say that they are a long time about it.

Attention to the Gastrointestinal Functions—There are those who urge that not only should constipation be vigorously combated but the colon should also be systematically irrigated, they are decidedly in the minority among

leading students of the disease. Since the recognition of the small amount of acid in the stomachs of some arthritics, the routine administration of hydrochloric acid as in achylia gastrica has become popular in some quarters, but I have seen no reported evidence of substantial accomplishment with this measure.

Treatment of Brucellosis—Goldfain (1939), in Oklahoma found a high proportion of arthritics had brucellosis also and concluded that treatment of the brucellosis helpfully influences the course of the arthritis. However, Greco and Freyberg (1941) have been unable to show a significant coincidence of the two diseases in Michigan, indeed not a one of the 25 patients with characteristic rheumatoid arthritis whom they studied had any evidence of brucella infection.

Sulfur Therapy—Freyberg *et al* (1940) and Abrams and Bauer (1940) have thoroughly laid this ghost.

Gold Therapy—In the third edition of this book I included gold among those drugs not meriting a full description and can only say that there seems plenty of reason to be still very skeptical of its value, but there is some stir in this field now in America and perhaps I should be remiss if I did not outline the use of the drug. Nevertheless it seems only fair that the reader be apprised of the cause of the renewed interest in gold therapy in our country. A good many years ago the French began using gold (to their own satisfaction at least¹) in tuberculosis and since they feel there is probably an association of some sort between tuberculosis and rheumatoid arthritis they logically tried gold in the latter also. Forestier was the outstanding leader in this work who, after numerous publications detailing successful employment of gold, came to this country and lectured on the subject. There followed a number of trials of the agent by American clinicians but the reactions were so frightening that gold therapy was quickly abandoned here. But the French and others on the Continent continued to report their satisfaction with the remedy and then the British took it up. But we still held off and finally the British lost patience with us and editorially as well as during personal visits to our shores let us know they thought we were not giving a good agent the fair chance it deserved. Of course had real foreigners pursued such tactics with us the result could only have been a strengthening of our opposition, but when friends with whom we have traditional ties in medical and many other fields so persistently nagged us it was only natural that here and there a clinic director said in effect 'Oh all right,' and began a new study of the drug.

RESULTS—Only one outstanding clinician in this country, so far as I know, has become really enthusiastic about the results and that is Cecil (1941) but Dr Cecil was also enthusiastic about the eradication of foci of infection a few years ago. Others also are reporting favorably, however but so far I have seen no study with adequate controls which was sufficiently extensive to be conclusive and no study even without controls in which the claims made abroad of cure or striking improvement in 80 to 90 per cent of cases have been substantiated. A typical conservative American report is that of Snyder *et al* (1939), who obtained improvement in 24 of their 50 patients (48 per cent). Many of the European cases are early, previously untreated cases—which leads me to recall again Miller's warning recently repeated by Angevine (1941), that perhaps 75 per cent of patients with rheumatoid arthritis will show improvement with no treatment at all.

REACTIONS—The present attitude in the United States is that gold therapy is so dangerous that it should be undertaken only in cases refractory to the more usual types of treatment and even then only if the patient and family understand the risk that is being taken. Cecil says that Forestier is impatient with this conservative tendency in us, but this is nothing new for we have always been more cautious in the use of potent drugs than the Continentals. The organs especially affected are those through which the gold is excreted—the kidneys, stomach and intestine. The following reactions occur: temporary increase in pain, skin eruptions, exfoliative dermatitis, edema, stomatitis, conjunctivitis, iritis, "gold bronchitis," gastro-enteritis, hepatitis with jaundice, albuminuria, acute nephritis, hemtopoietic damage (agranulocytosis, leukopenia, platelet reduction, purpura, aplastic anemia), neurologic and psychic manifestations. There is no way of anticipating, preventing or specifically treating these reactions. And some of the patients die. There are several reports in which 50 or 60 patients had been treated without a death, and Cecil said, in 1941, that there had as yet been no death in his series of over 200 cases, but it is generally conceded that about 1 patient in 100 treated may be expected to die from the treatment—though in fairness it must be said that this impression is gained chiefly from the 900 cases reported by Hartfall *et al.* in England, in some of which higher dosage than now current was employed. It is said that some type of toxic reaction occurs in about 50 per cent of patients but that about 15 per cent these reactions are only mild.

CONTRAINDICATIONS—The principal ones seem to be the following: pregnancy, severe anemia, history of purpura or agranulocytosis, ulcerative colitis, nephritis, diabetes, hepatic disease, congestive heart disease, chronic skin affections such as eczema (but not psoriasis), active tuberculosis, hypertension. Old age and arteriosclerosis do not seem in themselves to constitute contraindications. Parr and Slipton (1937), in Australia, considered that thin anemic patients with cold clammy skin should not be given gold therapy, but Tegner (1939), one of the advocates of the drug who visited us from England, does not agree with this. It would seem wise to withhold the drug in patients with an allergic history.

DOSAGE—Tegner says that in Europe one encounters great divergence of opinion regarding dosage. To me this fact seems in itself an indictment of gold therapy in its present status—do we have, or did we have even one year after they were introduced in their respective diseases, any doubt about the correct dosage of such drugs as the arsphenamines, atabrine or the sulfonamides? In the main on the Continent and even in England in some instances—for example the oft-cited study of Ellman and Lawrence (1938)—dosage has tended to remain higher than with us. Here in the United States it has been customary not to exceed a total of 1 to 1.5 Gm. of any one of the salts: gold thioglucose (solganal B), sodium gold thiomalate (myochrysine), sodium gold thiosulfate, the latter has been most often used. None of these drugs is Council accepted for use in arthritis. The drug may be injected intravenously or intramuscularly. The solution is prepared by dissolving the powder in triply distilled sterile water and injecting very slowly. The routine of Snyder *et al.* (1939) is representative. Two injections were given weekly for six weeks, a rest of a month or six weeks and then another course. If any reaction appeared injection was discontinued immediately and not renewed until all

Effect of Pregnancy—The observation that arthritis may recede before pregnancy has been made a number of times, but it was only a few years ago that Hench recorded the actual occurrences in a series of patients. Twenty of the 22 patients experienced striking generally complete relief during their 34 pregnancies, each experiencing it each time she was pregnant with one exception, that of a tubal pregnancy. The relief lasted for variable periods after delivery. I wonder that someone has not made a study of the effect of administering to arthritics the serum or plasma of normal pregnant women.

OSTEO-ARTHRITIS

(Hypertrophic Arthritis, Degenerative Arthritis)

This is the type of arthritis characterized by the presence of Heberden's nodes and the gradual onset, in individuals in or past middle age of stiffness and limitation of motion, some muscle spasm, and pain which may be both localized and radiating or referred. There is degeneration and thinning of the cartilage with new growth of bone around the edges of the joints involved, principally the spine, knees, knuckles, hips and shoulders, but without fusion of the articular surfaces. In contradistinction to rheumatoid arthritis, which is a disease of the synovial membranes and probably infectious, this is a non-infectious disorder of cartilage and bone. Very likely it is merely one of the phenomena of senescence, symptoms developing only when a joint that is wearing out continues to be subjected to chronic trauma, it has been alleged that the state is seen most frequently in the laboring classes but I do not know that a careful study would prove this to be true. Apparently osteo arthritis may occur as the result of an acute traumatization of a joint. Another form is that sometimes distinguished as "menopausal arthritis" in which women at the cessation of the menses whether this occurs normally or after castration, have the type of muscle and joint symptoms known as arthralgia. In this menopausal type, if the woman grows suddenly excessively stout it may be that pain and stiffness is experienced only in the knees when they are obliged to support this unwonted weight, but the symptoms are oftentimes present in other joints as well.

Osteo arthritis is the oldest disease of which we have indubitable record—in the skeletons of beasts that preceded man on the earth by several hundred millions of years, in the 'ape-men,' in earliest man, in man through all the ages.

THERAPY

The principles of treatment are the same as those which obtain in rheumatoid arthritis except that bony ankylosis and flexion deformity do not occur in the disease under present consideration and it is altogether a less virulent seeming malady. Indeed most of its victims have no symptoms at all, and in many patients—this is especially true in the menopausal cases—measures directed toward reduction in weight constitute the chief therapy. Latterly, the increasing use of estrogenic substances is giving relief in some of the menopausal cases (see article on the Menopause).

GOUT

Though there are many variants, the classical development of gout is about as follows. An individual—in 98 per cent of instances a healthy robust

the disease, Negroes are rarely affected. Patients do not die of the symptoms of the disease which we are so far able to recognize, but in the early stages they suffer greatly and are severely crippled later on. Gouty nephritis (the study of Coombs *et al*, 1940, indicates that the changes are the result and not the cause of the metabolic dyscrasia), and renal colic from urate stones or gravel, are recognized complications and there is strong suspicion of a greater frequency of vascular diseases in gouty than in nongouty individuals.

The distribution of the disease, both as to time and place, is very interesting. Gouty deposits have been found in the predynastic mummies of ancient Egypt, and in classical times it was very common in Greece and Rome, but at the present time the Mediterranean lands know it hardly at all. In the tropics of both hemispheres, as well as in China and Japan, it is extremely rare. England has suffered from it for centuries, but it now seems to be quite rapidly decreasing there, on the Continent, too, it is said to have decreased markedly since World War I. It has always been looked upon as of extremely rare occurrence in the United States, but recent studies indicate that far too many of our cases are being bandied about for many years with an incorrect diagnosis of rheumatoid or osteo arthritis, or a mixture of these two.

THERAPY

THE ACUTE ATTACK

At the height of the acute attack it is usually advisable to give a full dose of morphine or diacodid in order to bring quick relief from the severe pain. At the same time the first dose of one of the analgesic drugs should be administered, many men also give a dose of cathartic salts at this time.

Colchicine—The old galenical preparations, the wine and the tincture of colchicum, have proved highly unsatisfactory and are no longer used, but colchicine is looked upon by most men of experience as being a practically specific agent for relieving the pain of acute gout. The experience of Lockie (1939) is typical though it is greater than most men have had. In 75 private patients with proved gout all experienced marked relief from this drug about the time the diarrhea which it unfortunately causes set in. Dosage has to be more or less determined in each case though Lockie's good results were obtained with the routine employment of 1/60 grain (0.001 Gm.) doses. Hench (1941) uses either the 1/120 grain (0.0005 Gm.) or the 1/100 grain (0.0006 Gm.) tablets directing that two tablets be taken initially and then one every two or three hours (in severe cases even during the night) until pain is relieved or some gastro intestinal disturbance appears. He says that having learned his "diarrhea dose" a patient may sometimes obtain a satisfactory effect in a subsequent attack by taking one or two less tablets in the course. Colchicine has been used since time out of mind, indeed Lockie says it is mentioned in the Ebers Papyrus of 1550 B.C. but we have not the least notion how it works, it does not affect the uric acid level of either the blood or the urine.

The Cinchophens—These drugs (discussed in detail in Chronic Gout below) are used by a few men in the acute attack in place of colchicine and they are often markedly effective in relieving the pain. The usual dosage is 7½ grains (0.5 Gm.) three or four times daily. Ludwig *et al* (1938), of the Massachusetts General Hospital, state that they never use these drugs because of

the risk of inducing acute yellow atrophy and the fact that colchicine is equally if not more efficacious. Lockie's (1939) patients, too, found colchicine more effective than either the cinchophens or the salicylates. But Hench champions the cinchophens (see below). These drugs increase the uric acid output when first given, but in most cases a decrease takes place after a few days, perhaps to a level lower than the previous one.

The Salicylates—The salicylates also influence the uric acid output in a special way (see Rheumatic Fever) but it is generally recognized that they are less effective in relieving the pain of acute gout than either of the above two agents.

Local Applications—Hot or cold compresses rarely give relief but most patients like to keep the joint swathed in something during the attack. Massage and exercises are absolutely contraindicated. The diet at this stage should be strictly purine-free and the patient should be urged to drink much water.

CHRONIC GOUT

Dietetics—It has been felt by all observers since ancient times that obesity, alcohol, and gout are closely associated. In our own era the fact has been ascertained that purine-containing foods increase uric acid retention, the severity of symptoms, and the frequency of attacks. Therefore the prime requisites in the dietary management of gout have been held to be that obesity be combated, the use of alcohol restricted, and the purine content of the diet kept as low as possible consistently with a feeling of reasonable well being. Latterly, however, there are those who have begun to doubt the value of such a strict regimen as satisfaction of these requisites necessarily imposes. For example, Talbott and Coombs (1938), while favoring the currently accepted practices, were nevertheless obliged to report upon 2 patients who were worse when on restricted dietary than when not. Specifically, patient A while on the metabolism ward on a low purine diet during 3 periods totaling more than seven months had 12 attacks and severe gout on twenty-seven days, while during the following eight months at home on unrestricted diet he had 7 attacks and severe gout on eighteen days. Patient B during nine months in the hospital had 21 attacks and spent thirty-nine days in bed, in the succeeding fourteen months at home on an unrestricted diet including a moderate intake of beer and occasional indulgence in hard liquor he had 7 attacks and spent only seven days in bed. I do not know that anyone knows what to make of such things and it seems to me that at present we can still only proceed upon the basis of the low purine hypothesis, while hoping ardently that someone soon solves this riddle for us.

Combating Obesity—We cannot attack the problem as we would ordinarily do in obesity, i.e., by greatly restricting carbohydrate and fat consumption because this necessitates the allowing of an amount of protein which forces the taking of more of the purine-containing fowl, fish, and meats than is permissible. Therefore we can combat obesity in gout only by a constantly reiterated counsel of abstemiousness. Gouty individuals usually adore stuffing themselves, the attempt should always be made (and it will nearly always fail) to make them leave the table a little hungry still.

Alcohol Restriction—We like to believe that it is the heavy drinker or the debauchee who is most prone to gout, and therefore counsel against the "spree," but as a matter of fact few drunkards develop the disease. It

is the more or less steady but quite moderate drinker, especially of red wines and beer, who is apt to be gouty. For this reason total abstinence is the thing to be recommended.

The Purine free Diet—It is perhaps impossible to devise a truly purine-free diet that would be sustaining because even the common vegetables are not purine free. But the worst purine formers are fish, fowl and meats; these should be omitted from the diet during most of the time. The total proteins need not be reduced, therefore meat, fowl and fish restriction is compensated by the use of large amounts of milk, eggs, cheese and proteins in vegetable form. It has long been held that coffee, tea and cocoa should be withheld, but I am unable to find any evidence that these beverages do actually act as uric acid precursors. Perhaps this is just one of those things carried along in textbooks without real justification; patients would be immensely relieved if the page were torn out.

Actual Diet During the Attack—The patient is oftentimes miserable enough not to wish much food, this offers good opportunity for a little reduction in his weight. Have him drink all the water possible and permit him to partake only of the following (in small quantities): milk, milk toast with a little butter and sugar, the breakfast cereals (except oatmeal), potatoes and fruits.

Actual Diet in Chronic Gout—To accomplish the prescribing of a purine free diet as nearly as is practicable, the patient may be permitted to eat the normal diet for an adult (but in restricted quantities) provided that the following articles are omitted:

All meats: fish and shellfish, and fowl.

Soups: since nearly all soup stocks are made from meat.

Vegetables: asparagus, kohlrabi, lentils, mushrooms, onions, peas, radishes, shelled beans (kidney, lima, navy, soy), spinach and watercress.

Cereals: whole wheat bread, oatmeal, shredded wheat and other breakfast foods made from whole grain.

Condiments: all peppers and spices, catsup, mustard, horseradish and garlic. (Why? Is it just that the condiments increase appetite or does someone really know that they are more directly harmful?)

Now in order to obtain even reasonable satisfaction on such a diet the patient will have to take inordinate amounts of milk, eggs and cheese—and finally he will rebel. When this occurs allow him an occasional bit of bacon, chicken or lamb. Among the less harmful fish: Barborka, plaice, had dock, whitefish and fresh salmon. He also places oysters, crabs and lobsters among the "meaty" things least likely to cause an attack. A small portion of any one of the articles just listed may be given at one meal per day twice a week, and it might be well if the patient could always be held under this much control. Since this rarely happens, one should bear the following things in mind as the diet is expanded:

(a) The worst offenders among the meats are sweetbreads, kidneys, liver and brains, among the fish, sardines, herrings, anchovies, pike, cod and perch, among the fowl, squab and turkey.

(b) Boiled beef, from which the water has been twice poured off while cooking, has lost some of its purines and thereby become more acceptable.

(c) Soups are perhaps best not used at all because of their high content in extractives.

(d) Adding vegetables from the interdicted list is less harmful than adding meats, fish or fowl

Relative Amounts of Carbohydrate and Fat—Bartels (1930) has recently thought it was of advantage in a small group of patients to restrict fats as well as purine formers and to use relatively large quantities of carbohydrates. Certainly it seems worth while to give this regimen extended trial because Lockie and Hubbard, as mentioned earlier, have shown that fats tend to provoke gouty attacks.

The Cinchophens—Hench (1941) says that because these drugs are occasionally toxic they should not be used until others have been tried and failed but he is definitely convinced that they are the most effective of the lot and that their use is justified except for patients with hepatic dysfunction, or idiosyncrasy for the drug, or in those unwilling to take the slight risk but he also advises that certain precautions be taken. Here is his regimen at the Mayo Clinic: (a) he uses cinchophen in preference to neocinchophen because he believes it more effective even though somewhat more disturbing to the gastro intestinal tract, (b) the patient takes $7\frac{1}{2}$ grains (0.5 Gm.) three times daily for three consecutive days each week and continues this indefinitely with only such modifications as seem indicated in the individual case, (c) the following "precautions" are observed: patient must ingest 2 liters of fluid and liberal amounts of carbohydrate daily and take enough alkali (15 to 30 grains [1 to 2 Gm.] potassium citrate or 30 to 60 grains [2 to 4 Gm.] sodium bicarbonate three times daily) to prevent renal colic from precipitation of urate stones in an acid urine, patient must also report such unusual symptoms as anorexia, dyspepsia, nausea, loss of weight, pruritus or jaundice, and upon the appearance of any of these symptoms he must stop taking the drug at once and report for special therapy (carbohydrates intravenously, high carbohydrate diet, vitamin supplements, etc.)

A number of years ago Graham reported a patient who had been on such a regimen continuously for a period of six and a half years and doubtless there are many unrecorded instances in which the medication has been continued for an even longer time. It seems highly probable that the occasional reactions to the drug are upon an allergic basis, i.e., acute yellow atrophy being comparable in these cases to the acute agranulocytosis sometimes caused by amidopyrine. A mild reaction, omitted (but certainly inadvertently) from Hench's list of warning signs, is urticaria (hives), many men feel that when a patient develops an urticarial reaction to the ingestion of a drug he should never again be allowed to take a dose of that drug.

Many men feel that the danger of serious poisoning with the cinchophens outweighs the advantages derived from their use particularly as something can often be accomplished with other drugs and the disease progresses relentlessly despite all medication anyway.

The Salicylates—Satisfactory damping down of the symptoms is sometimes obtained with aspirin (acetylsalicylic acid). Ludwig *et al.* (1938) employ 60 to 80 grains (4 to 5 Gm.) daily for four days out of each week. Jennings (1937) found sodium salicylate, 80 grains (5 Gm.) daily with twice the amount of sodium bicarbonate for three or four consecutive days each week, just as effective as cinchophen. Hench (1941) suggests trial of sodium salicylate 60 grains (4 Gm.) and aminoacetic acid (glycine) 150 grains (10 Gm.) daily three consecutive days each week, basing the proposal on Quick's

(1933) report that aminoacetic acid augments the salicylate promotion of uric acid excretion

Colchicine—Some men feel that this drug is effective in warding off acute attacks Talbott and Coombs (1938) have followed Cohen's practice of giving 3 tablets of 1/120 grain (0.0005 Gm) daily for two or three days each week with satisfaction In several cases in which colchicine had been used in this way for more than two years no toxic symptoms had been observed

Thiamine Hydrochloride—Several investigators have been trying large doses of thiamine chloride but it seems to me in studying their papers that nothing of definite value has been added to therapy from this effort as yet I gain the impression from the recent reviews of Hench (1941) and of Sodeman (1941) that they are of the same opinion

Miscellaneous Drugs—It is not proved, indeed not even strongly indicated by results attained that the routine use of iodides or alkalis is helpful in the treatment of chronic gout Long ago it was proved that lithium salts have no value Acid, however, is indicated if the patient is on a purine poor diet since such a diet contains an excessive amount of alkali, the U.S.P. dilute hydrochloric acid may be used in a dose of 15 to 30 minims (1 to 2 cc) after each meal However, if the patient is taking cinchophen or a salicylate and accompanying it with an alkali to prevent stone formation the use of acids would of course be absurd

Smith has shown that there is no increase in uric acid excretion following the commonly recommended dose of live baker's yeast two three and five times this dose likewise gave negative results In his studies live yeast cells appeared in the feces in large numbers showing that they were not killed to any great extent in the gastro intestinal tract

The Allergic Approach—Allergists are beginning to interest themselves in gout and I think it high time There is nothing as yet to report except that of course they are concerning themselves with the possible allergens in the patient's diet rather than its purine content It seems to me that any physician might find it worthwhile looking upon his patient as at least potentially allergic (see Food Allergy) until proved otherwise

Treatment of Ulcerated Tophi—Hench (1941) says that if tophi break down intermittently and discharge urates for a long period they may be excised in order to prevent infection He says that thorough debridement results in prompt healing

Exercise—The value of exercise for the gouty individual has been long recognized Golf is unfortunately the only form of outdoor exercise that many city men can enjoy but the fact should not be overlooked that for individuals not too corpulent and whose arteries are not yet markedly sclerosed it is distinctly less valuable than the more vigorous forms of exercise It is sadly true that the streets of our industrial cities are becoming less attractive to the eye and less stimulating to the spirit as year follows year still a brisk walk is a brisk walk and as such is worth far more to an individual in need of exercise than is a round of golf as played on a crowded city course

The Spa—Spa treatment is endeared to us of old its value lying not in the ingestion of the mineral constituents of the waters but in the taking of so much water itself plus the other elements of a complete environmental change which render the resorts so valuable in the treatment of many chronic disorders

FIBROSITIS

(Myositis, Muscular Rheumatism)

This is possibly the most frequently encountered of the rheumatoid disturbances and likely deserves a more dignified position than it has attained in the literature, for there is no doubt about the incapacitating nature of an attack of fibrositis even though it is usually of only brief duration. Among 900 admissions in the arthritis clinic of the Hospital for the Ruptured and Crippled in New York, Traeger (1937) and his associates made this diagnosis in 262 instances, i.e., patients who presented with pain in or about the joints with no external evidences of joint pathology such as swelling, redness, fluid accumulation, muscular atrophy or deformity and without roentgenologic evidence of bone pathology or any laboratory findings of an elucidating nature. Sometimes there also occur deep-seated "fibrositis nodules," but according to both Traeger and Kelchner (1940) these are apparently less characteristic of the malady in the United States than in England. As the term indicates, fibrositis is an inflammatory reaction in the fibrous tissues of the body, and therefore the terms "myositis" and "muscular rheumatism" are misnomers since it is involvement of the interstitial tissues rather than of the parenchymal muscle tissues which causes the symptoms. Since fibrous tissue exists everywhere the possibilities for anatomic distribution in fibrositis are very great, but the pain, tenderness, and muscle stiffness (gelling phenomenon) which characterize it are most frequently encountered in the following forms: lumbago, torticollis or wryneck, an excruciating headache centering in the back of the neck, intermittent attacks of pain in any muscle groups associated or not with unusual use, stiffness or soreness of the joints after long periods of rest, interstitial neuritis in which the pain and tenderness are in the muscles and not along the nerve trunks, bursal fibrositis, which differs from bursitis in not being accompanied by increase in fluid in the bursa and definite limitation of motion, panniculitis, in which there is a loss of the elasticity of the skin, which becomes more adherent to the underlying tissues, fibrositis of the palmar fascia (Dupuytren's contracture). American writers like to include pleurodynia as simply a primary fibrositis but I notice that recent British authors, such for example as Nehgan (1939), do not specifically do so, I doubt if those who have had much experience with the epidemic form of this malady (see Epidemic Pleurodynia) would agree to its inclusion here.

THERAPY

Prognosis is good in these cases in the sense that crippling and deformity are not to be feared but it is common experience that to relieve a patient in an acute attack, or to shorten the course of a chronic siege, is easier to desire than to accomplish. Despite the venerable antiquity of this entity its therapy is still in a very uncertain state. Writers on the subject launch into discussions of the necessity to eliminate foci of infection, the value of vaccines, histamine iontophoresis, vitamin stuffing (the latest is vitamin E used in high dosage by Steinberg, 1941), diet, etc., in short the things are still being advocated here which have elsewhere proved passe (see Rheumatoid Arthritis). Of course the use of salicylates is indicated, but the two remedies which seem to be of greatest value are the old household ones of heat and massage. For methods

of applying heat see the article on Rheumatoid Arthritis Kelchner (1940) stresses the point that though massage should be begun lightly and gently it should be gradually increased until it becomes very vigorous, the idea being, it seems, to break up the fibrous accumulations. Massage should always be preceded by the application of heat, and it is to be expected that in the beginning it will increase the pain. Both Albee (1936) and May (1936) thought intestinal toxemia etiologically important and recommended colonic irrigations, even though I expressed an adverse opinion on this point it would be of no value since I lack experience in the disease. Kelchner says that when the pain is definitely localized, simple needling or else the injection of a few cc of sterile 2 per cent procaine hydrochloride solution, will bring relief.

Removal to a warm sunny climate is often very helpful to these patients. Traeger shrewdly remarks that perhaps most of the "arthritis" cases cured by a trip to Florida or Arizona are in truth only cases of fibrositis.

RICKETTSIAL INFECTIONS

(Typhus, Rocky Mountain Spotted Fever, Tsutsugamushi Fever, Trench Fever, Q Fever)

The rickettsial organisms, so named by da Rocha-Lima in 1916 in honor of the young American bacteriologist, Howard Ricketts, who had probably first observed them and who himself died of typhus fever, remain a puzzling group having some of the characteristics and attributes of both bacteria and viruses. But in recent years sufficient information has been accumulated with regard to them to warrant the present grouping of a number of diseases under the above heading in this book. These diseases have the following characteristics: (1) They are of world wide distribution and differ somewhat in their symptomatology in different regions, but they are nevertheless sufficiently similar that all the others must be differentially eliminated before making a diagnosis of any one of them. (2) The organisms are conveyed in some instances from man to man and in others from animals to man, an insect being the intermediary host and vector in all cases. (3) The essential pathology in the rickettsioses consists in necrotizing damage to blood vessels in various portions of the body. (4) The characteristic clinical features of these infections are (a) sudden onset with chills, fever, gastro intestinal symptoms and headache and pains all over the body and great restlessness with often other manifestations of central nervous system involvement, (b) the appearance of a rash some time within the first few days, (c) relatively few complications, (d) a positive Weil-Felix reaction, (e) death or termination by crisis with few sequelae.

Classification of these diseases is still somewhat confused (Blumer, 1941, says that more than 90 names have been applied to classical typhus alone), but I think the group can be presented with sufficient clarity under the following heads: epidemic typhus, endemic typhus, Rocky Mountain spotted fever, tsutsugamushi fever, trench fever, Q fever. The therapy and prophylaxis of all these entities may be satisfactorily considered simultaneously. It

is of interest in passing to note that evidence is accumulating that trachoma is a disease of rickettsial origin and that some observers regard psittacosis (*q v*) as a rickettsial rather than a true virus disease, while some students of thromboangitis obliterans (*q v*) feel there is some connection between that disease and typhus

EPIDEMIC (CLASSICAL OR "EUROPEAN") TYPHUS FEVER

(*Louse borne Rickettsial Fever*)

Epidemic typhus fever is an age-old decimator of the dirty majority of mankind, though it was not recognized as a clinical entity until the sixteenth century and was not clearly differentiated from typhoid fever until the middle of the nineteenth century. The causative organism, transmitted from man to man by the body louse is *Rickettsia prowazeki* named for one of da Rocha Lima's coworkers who, like Ricketts died of the disease. This form of typhus is in the main a disease of the cooler portions of the earth but it also occurs in North Africa, Egypt and in the cold season even on the Ethiopian plateau. Gear (1938) says that it is a major public health problem in the Union of South Africa. Cases are occasionally seen in Mexico and parts of South America. The chief endemic foci are in the Balkan States, northern Italy, a number of spots in eastern Europe, Russia, Siberia, northern China and Ireland. Practically all the countries of the north temperate zone have had severe visitations of this disease. The typhus years in the United States were 1812, 1830, 1847, 1865, 1881, and 1893, these outbreaks were usually confined to recently arrived immigrants in the seaboard cities and very probably were mere importations of the disease. All wars have felt the ravages of typhus, probably the greatest havoc was wrought during the 'Thirty Years' War in the seventeenth century, and next during the Napoleonic campaigns. In World War I the French, British, and American armies on the western front were practically typhus free only because the Germans and Austrians were fiercely fighting to keep it away from their front lines, their rear being heavily attacked by it from Russia. Eastern Europe and the Balkans suffered severely during and after the war, 10 000 000 cases being alleged to have occurred in Russia alone in the period 1919-22, the mortality in the epidemics averaged 20 per cent with a range of 5 to 70 per cent. This form of typhus is distinctly more prevalent during the winter months, mortality is lowest in children and highest in the aged. The incubation period seems to be from one to two weeks. An oft repeated adage, well characterized by Dyer (1941) as 'rather tiresome but too truthful' is that the extent of typhus at any given time is a current measure of human wretchedness. Close quarters, malnutrition and cold invite it surely, we know it now to be active again on the Continent but the censorship prevents accurate knowledge of the extent of the epidemics.

The interesting Brill disease, an endemic mild variety of typhus existing in the larger northeastern seaboard cities of the United States is apparently confined to individuals who emigrated from the typhus ridden regions of southeastern Europe. It has not been possible to detect man to man or flea or louse to man transmission of this disease. Zinsser and his associates were of opinion that these cases are recrudescences of European typhus fever acquired at an earlier time in an endemic Continental focus. It is definitely a mistake to refer to cases of the endemic typhus of our southern states (see

below) as Brill's disease, even though the latter does have a seasonal prevalence more like that of endemic than classical epidemic typhus.

The symptomatology of a fulminating case of epidemic typhus is about the following. Usually, with few prodromata, there is a sudden chill and rise of temperature which is accompanied by nausea and vomiting and a headache, sometimes there are aching pains throughout the body also. The rise in temperature is accompanied by a proportional increase in pulse rate and in the severity of the headache, but the gastro intestinal symptoms disappear early. The temperature often reaches 105° F (40.5° C) on the second or third day, to remain with remarkably little daily remission until the close of the attack. On the fourth to seventh day a maculopapular rash appears which changes from pink to red, then purplish brown, it involves usually all of the body but is often very sparse or absent on the face and neck. On reaching full efflorescence, some of the spots become hemorrhagic and purpura appears irregularly. The patient experiences sleeplessness from the beginning, which gives way to wild delirium, and in severe cases the delirium passes into a state of "coma vigil" in which the sufferer lies in a relaxed position though the body is usually twitching, the eyes are wide open and staring, there is a low muttering delirium, and a rapid thready pulse. Oftentimes there is other early evidence of central nervous system involvement such as tinnitus, vertigo, and deafness. There is usually a loose cough almost from the beginning. Small areas of spontaneous necrosis of the skin are not rare. The crisis is reached on the thirteenth to eighteenth day, after which there is a rapid disappearance of all symptoms, though the discoloration following the rash usually fades gradually and convalescence may be very protracted. The two complications chiefly to be feared are secondary bronchopneumonia and thrombosis of the large vessels. The Weil-Felix agglutination test is of not very great value as an early diagnostic aid for the reason that it unfortunately does not become positive until the rash has appeared.

ENDEMIC (MURINE) TYPHUS FEVER

(*Flea borne Rickettsial Fever*)

This form of typhus, now recognized to be a disease of considerable importance in the United States, differs radically from the classical form of epidemic typhus (see above) in several respects. In the first place, the great reservoir of the disease is not in man but in the common gray wild rat. In the second place, it is not conveyed by the body louse but by the rat louse and the rat flea, particularly the oriental rat flea *Xenopsylla cheopis*, which keeps the disease going in rats and occasionally conveys it to man. In the third place, the disease does not occur in man in large epidemics under conditions of privation and want but remains endemic, the cases at most grouping themselves about locations especially heavily infested with rats, such as shops, groceries, grain depots, warehouses, and at times the lowest class of dwellings. And finally, unlike epidemic typhus, which occurs predominantly in the winter, endemic typhus though occurring throughout the year reaches its very definite peak in the summer months. Most of the patients are young adult white males and until recently nearly all cases have occurred in small towns and cities, but latterly the incidence has been rising in rural areas, which may be a reflection of the establishment

of the disease in some rodent other than the rat, a number of species have been found susceptible in the laboratory and Brigham and Dyer (1938) once trapped an infected field mouse on a farm.

Just how long endemic typhus, whose causative organism is *Rickettsia prowazekii mooseri*, has been prevalent in this country we do not know, but it was first recognized in Georgia by Panlin in 1913 and has been reported with increasing frequency since Maxcy's intensive studies began in 1923. In the ten year period, 1929-1938, the number of reported cases was 11,427, but Kemp (1939) undoubtedly voices the consensus in saying that the true number of cases is very likely greater than that reported. Practically all of these cases have occurred in North and South Carolina, Georgia, Florida, Mississippi, Alabama, Texas and southern California, with a few scattered cases in other southern states, and a very few cases indeed elsewhere in the country. This distribution is certainly not that of the common rat, and it may not be purely climatic for there is the flea also to consider. *Xenopsylla cheopis* was originally found only in seaport cities, then it moved inland throughout the South and now it has been reported to be established at Ames, Iowa (Roudabush, 1939) and in Youngstown (Ewing and Fox, 1938) and Columbus (Runner, 1941) in Ohio. It is considered likely that as *X. cheopis* increases its territorial invasion, endemic typhus will go along with it. While much of the investigative work on endemic typhus has been done in the United States, the disease occurs widely throughout the world. Manchuria, Malaya, Syria, Greece, France, Africa, China, Indo China, Hawaii, and probably, according to Wolbach (1940), the Philippines. The disease "tindhillo" in Mexico is apparently at times endemic typhus and at other times louse-borne epidemic typhus.

The symptomatology (including the Weil-Felix reaction), duration and course of endemic typhus are the same as of epidemic typhus (see above), but the attack is much milder and complications rarely occur. In the age of greatest incidence (young adults) mortality is between 1 and 2 per cent, according to Gordon (1940) it is 5 to 7 per cent in those between forty-five and sixty-five years and about 30 per cent in those above sixty-five.

ROCKY MOUNTAIN SPOTTED FEVER

(Tick borne *Rickettsial* Fever)

This disease was formerly thought to be peculiar to certain discrete localities in the states traversed by the Rocky Mountains having its greatest frequency in Idaho and Montana. We now know, however, that it occurs in the eastern states in the South, and in the central tier of middle western states, very likely increasing knowledge of the disease will disclose its presence throughout the entire country. The causative organism, *R. rickettsii* (or probably more properly, *Dermacentor exenus rickettsii*) is hereditary in wood ticks in the West where the tick often conveys it to man, in the cases often referred to as the "eastern" type of the disease the common dog tick is the vector. Both the wood and dog ticks are found on a wide variety of animals, horses and mules, rabbits, deer, wildcats, foxes, squirrels, opossums, badgers, porcupines, skunks, coyotes, wolves, hogs, woodchucks and weasels are so far indicted. According to Wolbach (1940) altogether ten ticks are proved or potential vectors and all North American rodents, man, monkeys, and dogs are susceptible to more or less severe infections. In the West, the disease occurs

most frequently in spring and early summer and its victims are most often men whose occupations or pleasurable pursuits take them into infested country, but cases occur also among women and children of families living in such areas. In the East, many of the cases are seen among campers and children, the latter because of their intimate association with dogs. Definitely, then, Rocky Mountain spotted fever is a rural disease.

The incubation period ranges from two to fourteen days in most instances, though Carey (1939) records a case in which the tick was removed on the first day of symptoms. Parker (1938), who has had an enviable experience with this disease, says that the shorter the incubation the more likely is the attack to be severe. In average cases, either with or without a prodromal period of vague illness for a few days, the patient comes down with initial chill, high fever, very severe headache and pains all over the body, and extreme restlessness and insomnia. There may be obstinate constipation or diarrhea, distention of the abdomen, and vomiting, retention of urine with incontinence occurs at times. Often, according to several observers there is a definite body odor. Cyanosis is frequently present and sometimes edema of the extremities and face also, the spleen may be enlarged, nosebleed, photophobia, and conjunctival injection, and a dry hacking cough without definite signs in the lungs, frequently occur. Typically, the rash appears on the second to the fourth day. It usually starts on the wrists and ankles, less commonly on the back, and may be preceded by a mottled appearance of the skin. Rose-colored, and beginning in either macular or papular form, it usually spreads rapidly as a macular rash to all parts of the body surface and the buccal and nasal mucosae. At first it disappears on pressure but later it persists and becomes darker and more or less bluish. Parker says that the larger and more scattered the spots are and the brighter their color remains, the better the prognosis, spots which remain pinheads often become rapidly darker and in such cases the rash soon becomes hemorrhagic and more or less confluent and blotchy. Sometimes in milder cases the spots appear in several successive crops. In very severe cases sloughing of dependent portions of the body, such as the external genitalia, may occur and there are evidences of considerable involvement of the central nervous system, such as delirium, convulsions, stupor, coma, etc. The average duration of the fever, usually characterized by morning remissions, in nonfatal cases is two to three weeks, termination being by lysis, convalescence is usually extremely slow. In fulminating cases death may occur before the rash appears, in less rapidly fatal cases the patient dies on the sixth to twelfth day. There is an abortive form of the disease which is usually stormy but with a very quick recovery, and there are other patients who are able to remain ambulatory throughout the attack, the likelihood is great that many subclinical cases also occur. Of diagnostic aid are the Weil-Felix reaction (usually becoming positive between the eleventh and nineteenth days) and the fact that the blood of the patient injected into guinea-pigs produces fever, sloughing of the scrotum, and death. Parker says that such sequelae as the following have occurred: deafness, impaired vision, insomnia, neuroses, diminished endurance, unfavorable progression of degenerative diseases. Brunsting (1939) and Cohen (1940), have each reported a single case which relapsed once. A few second infections are on record. Hampton and Eubank's (1938) review of 2036 cases showed a fatality rate of 19.4 per cent in the Western cases and

18.1 per cent in the Eastern cases this indicates only however that mortality is about the same for the disease throughout the country but does not reflect the fact that in certain areas such as the Bitterroot Valley section of Western Montana and certain localities in Washington Oregon Idaho and Wyoming the death rate is extremely high averaging according to Parker (1938) 80 per cent for adults and 97.5 per cent for children

The following diseases are very closely related to Rocky Mountain fever if indeed they are not identical with it. Mediterranean eruptive fever (*fevre boutonneuse*) São Paulo and Minas Geraes exanthematic typhus spotted fever of Tobia (Colombia) and the relatively mild South African tick bite fever. In both *fièvre boutonneuse* and South African tick bite fever a primary sore develops at the site of the bite

TSUTSUGAMUSHI FEVER

(*Mite borne Rickettsial Fever*)

This disease occurs in Japan (where it was first described as Japanese river fever) Formosa the Philippines Indo China British Malaya the Netherlands Indies the island of New Guinea (Gunter 1940) and North Queensland in Australia (Heaslip 1941) Lewthwaite and Savor (1940) seem to have established that scrub typhus and rural typhus in Malaya are really tsutsugamushi fever. A great reservoir for the disease apparently exists in rats voles and bandicoots. Like Rocky Mountain fever (see above) which it seems to resemble very much clinically tsutsugamushi is a rural disease the latter differing from the former chiefly in the following particulars: (a) The causative organism *Rickettsia tsutsugamushi* (*R. orientalis* *R. aliamushi* etc.) is transmitted by a mite. (b) A necrotizing lesion appears at the site of the bite and there is adenitis of the drainage area and sometimes of other areas as well (the exception here is Malayan rural typhus in which this lesion is rarely seen and it is said not always to occur in Formosa either). (c) The rash seems often to make its appearance first on the trunk but in many of the dark skinned natives in the affected regions it is not possible to make out a rash at all. Mortality varies widely in reported series of cases between 2 and 40 per cent, being very much bigger in Europeans than in natives. Reinfections are not uncommon but are usually mild.

TRENCH FEVER

(*Shin-bone Fever*)

Trench fever is a practically nonfatal but extremely debilitating disease transmitted by the body louse. It is considered that *Rickettsia pediculi* is probably the causative organism but since no experimental animal has been established and active cases in the human are not being seen currently it has not been possible to prove the fact. Graham of the British Expeditionary Force first described trench fever as a new disease in 1915 though it may have existed as an unrecognized entity long before that time in various parts of the world some observers indeed considered it a revival of medieval sweating sickness. Swift says that the condition was probably endemic in Russia and was disseminated to all the fighting fronts in World War I by the movement of German and Austrian troops. In 1917 Grieseson stated that

at one time 60 per cent of all patients in British military hospitals had trench fever. It is an interesting speculation how much sooner that war might have terminated had it been possible quickly to control this malady. Braslawsky (1934), of Kiev, looks upon trench fever (which he prefers to call "five-day fever") as existing endemically in certain parts of Eastern Europe, if this is true, and if World War II bogs down into a static phase in that territory, we may again see trench fever spreading over the Continent. In the winter of 1940, Templeton remarked upon the occurrence of symptoms resembling those of trench fever in the bomb shelters of England.

The prodromal symptoms of this disease are not characteristic but the onset is sudden, i.e., all of the symptoms have usually developed in twelve to twenty-four hours from the first appearance of any one of them. There is chilliness or a definite chill, prostration of varying intensity, rise of temperature to 103°F (39°C) or more, anorexia and sometimes vomiting and sweating, frontal headache and severe pain "behind the eyes," and generalized pain and tenderness in both muscle and bone, the especial severity of this latter symptom in the lower legs, particularly at night, gave the infection its popular name of "shin bone fever." A macular rash occurs on chest and abdomen. The course of a particular case has not been predictable, sometimes there was but one bout of fever which was over in a few days, or the attacks recurred regularly at three to seven-day intervals, or the case ran a protracted typhoid-like course. The tendency to relapse months or even years after the initial attack was typical of the disease and a too early return to active work was almost certain to cause a recrudescence of symptoms. The bronchitis present in some cases was not of serious moment, but we do not know as much as might be desired of the extent of the circulatory involvement during the earlier stages of the attack. Certainly many of the cases of "effort syndrome" of those days had their inception in a bout of trench fever.

Q FEVER OF AUSTRALIA AND AMERICA

This is an extremely interesting "new" entity. In 1937, Derrick reported among abattoir workers and dairy farmers in Queensland 9 cases of a disease which resembled mild typhus but differed from it in the absence of a characteristic rash and the consistently negative Weil-Felix test, severe and persistent headache and a comparatively slow pulse rate were outstanding symptoms. Burnet and Freeman have shown that the organism since designated *Rickettsia burneti* is the causative agent and it has been established that a reservoir of the disease exists in the bandicoot and that a certain tick is the natural vector among these animals. There are no records of this tick attacking man (though Smith, 1941, states it will do so readily in the laboratory) and a history of tick bite has not been a feature of the human infections, however, the affected occupational group has been exposed to animals and inferentially contracted the disease by contact with ticks or fresh tick dejecta. In the United States, Davis and Cox (1938), and others since, have isolated from wood ticks in the West the organism which is now called *R. diaporica*. In the same year, Dyer reported an attack of disease in a laboratory worker who had had some contact with this organism, later, this "Nine Mile" fever (so designated from the site in Montana from which the original batch of infected ticks had come) appeared in epidemic form.

(15 cases) in one of the United States Public Health Service laboratories in Washington, D C., in a building housing rickettsial studies. In this outbreak, carefully studied by Hornibrook and Nelson (1940) and Dyer, Topping and Bengston (1940), the presence of central pneumonitis which was revealed only upon roentgen examination has provoked interesting speculation regarding the relationship of this disease to the cases of "atypical pneumonia" and "acute pneumonitis" which have been reported with increasing frequency in recent years. Hesdorffer and Duffalo (1941) have put the matter to the test in a single case and found that the patient's serum agglutinated *R. diaporica*. Another disease which is likely to make differential diagnosis increasingly difficult in this field is adult toxoplasmosis, an entity previously unrecognized until Pinkerton and Henderson (1941) reported their 2 fatal cases, this disease, however, is caused by the organism known as *Toxoplasma* and is therefore not a rickettsial infection.

The total evidence to date indicates that Australian and American Q fevers are closely related if not identical.

THERAPY OF THE RICKETTSIAL INFECTIONS

The treatment of all these diseases is entirely symptomatic. The patient should be given plenty of easily digestible food and much fluid for in many instances he is facing a sledge-hammer type of toxic attack which quickly hatters thin his reserve of stored energy. The mouth must be kept clean else it becomes very foul and an easy prey to secondary infection, liquor antisepticus of the N F is a good preparation to use for the purpose. For treatment of the cough see the article on the Common Cold. All authorities agree that it is usually necessary and advisable to control the insomnia of fulminating attacks by the use of morphine. If this drug is not being used some less powerful analgesic will be indicated to combat the headache, phenacetin (acetphenetidin) in a dose of 5 grains (0.32 Gm.), or acetanilid, 3 grains (0.2 Gm.), either of these may be reinforced by the addition of $\frac{1}{2}$ to 1 grain (0.03-0.06 Gm.) of codeine sulfate and one of the barbiturates, such as phenobarbital, $\frac{1}{2}$ grain (0.03 Gm.). The cooling sponge bath is of course indicated if there is hyperpyrexia. Martin (1940) well stresses the importance of special care to avoid bed sores as the skin is very prone to ulcerate and become gangrenous in these affections. He also considers that because of the eadarteritis which characterizes the pathology of a rickettsial attack, blood transfusions should be given only if they seem "imperatively necessary."

I find recorded trials of the sulfonamides in Rocky Mountain spotted fever, in Q fever, and in tsutsugamushi fever, in all instances they either were not helpful or seemed actually to be harmful to the patient (Pilcher, 1938, Gunther, 1940, Martin, 1940, Campbell and Ketchum, 1940, Hornibrook and Nelson, 1940). In 1917, Richter reported collargol to be of specific value in trench fever. Sweet and Wilmer also had good results in the 35 cases in which they used the drug but they were hesitant to ascribe all the credit to this therapy in a disease so variable in its course as trench fever. Collargol is given in 1 per cent solution, 10 cc. being injected intravenously at two- or three-day intervals, with care to prevent infiltration of the extravascular tissues, a pronounced febrile reaction follows the injection. Coalescent serum has had no trial to my knowledge. According to Gunther, autohemo-

therapy (see Index for methods) has been successfully used by Babalian in a few cases of tsutsugamushi fever

PROPHYLAXIS OF THE RICKETTSIAL INFECTIONS

Protection Against Lice—This is of importance in epidemic (European) typhus and in trench fever, the measures are those employed in ridding and maintaining the body free of lice (see Lice, in Index)

Protection Against Mites—This is important in tsutsugamushi fever Heaslip (1941) says that maintaining cleared areas around dwellings is helpful in keeping down the incidence in families, but since the disease is usually contracted by men who must go into mite infested bush country, and because the wearing of fully protective clothing is impossible in the hot lands where tsutsugamushi reigns, it does not seem to me there is much hope of protecting against mites. Gunther (1940) says that none of the preparations advocated for anointing the body is really useful

Protection Against Rat Fleas—This is important in endemic typhus, one of the two rickettsial diseases with which we are chiefly concerned in the United States, and is largely a matter of educating the public in the affected regions to fight the rat as a dangerous enemy to health. Of course there is no thought of attempting complete eradication of the rat population but Bowdoin and Boston (1940) find the following measures feasible in their campaign in Georgia: (a) educational meetings designed to acquaint the people with the nature of the transmission of the disease, (b) removal of rat harborage such as trash, rubbish and old lumber piles, and insistence upon the use of garbage cans with tight fitting lids, (c) a rat extermination program in areas known to be foci, (d) and finally, and most important of all, rat proofing measures designed to separate rat and man permanently

Protection Against Ticks—This is important in both the Eastern and Western forms of Rocky Mountain spotted fever. Of course, as Parker (1938) well says, the best method of avoiding infection is to stay away from regions known to be heavily tick infested, but for a large part of the population this is impossible. Dogs should be frequently deticked, keeping them clipped during the summer will facilitate this, and dusting frequently with flea powder is also helpful. Children associating with dogs or resident in the country, or even playing on vacant brush grown lots in the city, should have their heads, necks and bodies examined several times daily. The important thing is to get the tick off at once. Remove him with forceps or while wearing gloves because crushing him in the fingers is dangerous. Sometimes in pulling him away the mouth parts remain in the wound site, which is undesirable, therefore some men advise forcing the tick to detach himself by applying ether, benzine, turpentine, or tobacco juice to him. Wilson (1940) has described the following simple method of accomplishing the same thing. Strike an ordinary household match, shake it out as soon as it flares and apply the hot head to the rear end of the tick, he will quickly withdraw his head. Do not apply the flaming match for this will kill the tick before he can withdraw. Apply tincture of iodine to the wound site, preferably boring in a toothpick end saturated with it, or apply a silver nitrate stick.

When tick infested areas must be visited by men necessarily engaged in outdoor work or by campers, hunters, etc., the following precautions (con-

densed from Parker's excellent account) must be observed (a) Women as well as men should wear trousers and the tick must be prevented from reaching the bare legs by wearing socks and high boots, leggings or puttees over the trouser legs (b) A sharp watch must be kept for ticks crawling up the outside of the clothing (rough clothing will slow him up but smooth clothing will give him a less secure hold) and the hand should be frequently passed across the back of the neck to feel for ticks that may have reached that first area of exposed skin (c) The entire body and the inside of the clothing should be thoroughly examined at least twice daily (d) Upon retiring remove all clothing and place it far enough away that ticks cannot crawl from it to the bed (e) Ticks tend to gather in the brush along old trails, in sage brush and in the grassy strips in the middle of little used roads

Protective Vaccines—Dyer (1941) well emphasizes the point that specific immunization is feasible in diseases transmitted from man to man because such immunization is cumulative since each protected individual reduces the sources of infection by one, but in diseases in which an animal other than man is the reservoir of the infection this cumulative factor is lacking. Logically, then, in *tsutsugamushi fever*, and *endemic typhus*, in both of which the known rodent reservoir is of great importance, one would not expect much to come of efforts at preventive vaccination. Indeed, it is considered that even if an effective vaccine were available against endemic typhus its use against the disease in our own South would not be practicable because the cases are so relatively few. The incidence of *tsutsugamushi fever*, however, is very high in certain restricted areas in the tropical orient and therefore a vaccine might be feasibly employed. Such a vaccine has recently been used successfully in volunteers by Kawamura *et al* (1939), but there has so far been no report of extensive field trials.

In *Rocky Mountain spotted fever*, in which there is also a great animal reservoir, the existence of areas of very high endemicity and virulence in the West has also warranted studies of a vaccine. At its station in Hamilton, Montana, the United States Public Health Service has been making and using such a preparation for many years. Each cc of this vaccine contains the killed virus of $1\frac{1}{2}$ ticks. Usual dosage is 2 injections of 2 cc each, given five days apart and repeated each year, though in some areas of exceptionally high case fatality 3 injections have been used. This vaccine has always been very expensive to make and the amount available limited, but there are recent indications that some of the difficulties are being overcome. Parker (1941), summarizing the experience of fifteen years, is able to show very definitely that persons vaccinated the same year they become infected with highly virulent strains are sufficiently protected to lessen greatly the severity of the disease and to insure recovery, against less virulent strains full protection apparently sometimes occurs. The greater number of years a person has been vaccinated the greater his protection, children being in any case more protected than adults, it seems. Insufficient data are available upon which to form an opinion of the protective value of this vaccine in the Eastern form of the disease.

In *epidemic (European) typhus*, of which man is the sole animal reservoir, much might have been expected from vaccines but it was not until very recently that a sufficiently innocuous preparation became available for mass immunization. Now, as a result of the yolk sac and agar tissue culture yolk

sac methods employed by Cox, Zinsser, Castaneda and their associates, we have satisfactory immunizing materials. Extensive trials are known to be under way on the Continent, in China and in Bolivia but we do not know as yet what measure of success they have attained. However, the studies in this country and in Mexico, using volunteers, are convincing, and Col Simmons (1941) has said that the U S Army will be routinely immunized should the need arise, a statement recently substantiated in War Department Circular Letter No 3, Jan 31, 1942.

In trench fever and in Q fever there has been no talk of vaccines as yet

SCARLET FEVER

Scarlet fever is an acute infectious disease in which it has long been suspected that some type of streptococcus is the etiologic agent, but whether or not it is the *Streptococcus haemolyticus scarlatinae* of the Dicks has not been settled to the satisfaction of all observers. It is granted that scarlet fever has been induced by the injection of this organism in the human but those who object to full acceptance of its specificity maintain that at most it can be only one of several strains capable of acting in the causative role, for the reason that scarlet fever may also follow infection with streptococci from erysipelas and puerperal fever, and that these streptococcal diseases have followed infection from typical scarlet fever. These questions and others of equal interest, to be referred to later, which have arisen in recent years have redirected our attention toward this very old malady which I am afraid many of us had been thinking was already well along toward achieving the epidemiological status of diphtheria.

Scarlet fever is very much more common during the first decade of life than during any other period, and though occurring sporadically it has a strong tendency to become epidemic, the seasonal incidence being greatest in the school period of September to June. It is much more often food borne (milk or milk products) than is diphtheria. The virulence of the disease varies, mortality among children in the various epidemics being from 15 up to as high as 90 per cent, after the eighth year, mortality rarely runs above 3 to 4 per cent, and indeed in recent years the death rate has been very low in all age groups in most parts of the world.

The typical case is characterized, after an incubation period of three to eight days, by sudden onset with nausea and vomiting, high fever, sore throat, leukocytosis, general adenopathy, and the appearance within twenty four hours of a generalized, scarlet, maculopapular ("goose flesh") rash on the body and a punctate eruption on the roof of the mouth. The 'strawberry' appearance of the tongue is regarded as characteristic of the disease. nosebleed is not uncommon. The temperature and other symptoms usually begin to subside gradually within five to seven days, and a few days after the disappearance of the rash the period of desquamation begins. It is during this period of desquamation, which lasts for several weeks, that the secondary complications are most likely to arise, there are a great many of these but of those most frequently seen the most severe are peritonsillar and retropharyn-

geal abscess cellulitis of the neck, sinusitis, otitis media and mastoiditis nephritis, and orchitis

There are several atypical types of the disease and two definitely recognized malignant types (both fortunately rare nowadays) the fulminating type in which death occurs from acute failure of the heart almost before the symptoms of the disease have appeared and the septic type in which the original process in the throat quickly involves the nose and the larynx and trachea with death from sepsis

Scarlet fever is one of the diseases of which the great Sydenham (1624-1689) has left a first hand account, separating it from measles and giving it its present name its confusion with measles however, persisted for a long time after his day Following the period which corresponds roughly with the American War for Independence in the late eighteenth century scarlet fever spread rapidly over both hemispheres and now occurs all over the world but is extremely rare among natives of Africa and India

THERAPY

Nursing Care and Diet.—Mild cases of scarlet fever require practically no treatment though the physician and nurse will often be greatly taxed to keep the child in bed until the danger of delayed complications has passed Perhaps enforced bed rest of three weeks is ideal but in the 80 per cent or more of extremely mild cases seen nowadays this is practically impossible of accomplishment and is usually considered unjustified Children will usually take large quantities of fluid quite readily if offered in the form of lemonade Diet is usually maintained in the beginning on the liquid basis with milk predominating but the causal relationship of a full diet to nephritis in this disease has not been established It is now agreed that the more liberal diet has proved the better procedure Bauer (1936) writes Milk cooked cereal and stewed fruit must be given even in the acute stage Baked potatoes gelatin and junket and orange juice within reason can augment this diet When the fever subsides a full child's diet may be started including meat and eggs After desquamation begins the patient is much relieved by the application of ordinary petrolatum to which a small amount of phenol has been added, but it is well to keep the proportion of phenol below 0.5 per cent if the entire body is to be anointed I have seen a case of mild kidney injury caused by one application over the entire skin surface of an ointment containing 2 per cent of phenol The complications must be treated as such when they make their appearance Isolation of patient and nurse is to be maintained throughout (a) toilet facilities for their exclusive use (b) sleeping quarters for nurse to sickroom or in room adjoining which is to be entered by no one else (c) physician to be gowned while in sickroom (d) dishes to be sterilized before they are taken from the room (e) garbage to be placed on fresh newspaper outside room and immediately bundled and burned by an elderly member of the family (f) all linens, etc. to be sterilized in the room before being sent to the laundry

Antitoxin—The Council passed product at present available in the United States is prepared after the method of the Dicks by immunizing horses by injecting the soluble toxin of strains of hemolytic streptococci that have produced experimental scarlet fever in human beings It is given intramuscularly

only in extreme cases intravenously, the dose varies with the different manufacturers. In recent years the early enthusiasm with which the antitoxin was hailed has so considerably waned that the following points I believe now comprise the consensus among conservative unprejudiced observers.

(a) Early administration of antitoxin usually causes subsidence of fever and the disappearance of the rash and other toxic manifestations but carefully controlled studies do not show that the incidence or severity of the complications is lessened with its great regularity.

(b) The likelihood of inducing serum sickness may easily cause a longer illness than would be suffered in the average case without the treatment.

(c) Severe reactions to the antitoxin itself were of frequent occurrence with the earlier preparations but with the concentrated antitoxins now on the market they do not occur nearly so often. It is of interest to note that Banks (1936) found constitutional reactions following intraperitoneal injection of the earlier unconcentrated type of serum to be very rare and mild; this was true even when he used batches known to cause frequent and severe reactions when given intravenously. He suggested, however, that serum preserved with 0.5 per cent phenol may be unsuitable for intraperitoneal injection for a batch of such serum gave rise to abdominal pain, tenderness and rigidity.

In the letter of the National Research Council Committee to the Surgeon General with regard to the treatment of military personnel it was recommended (J. A. M. A. Feb. 5, 1941) that antitoxin be given in moderately to extremely severe cases if the patient is not hypersensitive to horse serum; in other words, unless a type of scarlet fever much more virulent than is currently being seen in civilian practice develops in the army camps, antitoxin will not be much used in treating our soldiers.

Convalescent Serum—Pooled human convalescent scarlet fever serum has been in use here and there quite steadily since its reintroduction by Reiss and Jungmann in Germany in 1912; theoretically it has the distinct advantage over antitoxin in presumably containing antibodies against the actual causative organism, be that what it may, and is not an agent whose production rests upon the use of an antigen of an organism whose true etiologic role is not yet fully established. And now, in recent years, the organization of several municipal centers for the collection, preservation and distribution of such serum is enabling us to assess its value from the vantage point of practical employment in large numbers of cases. In 1941 the Council on Pharmacy and Chemistry accepted such serum from the following centers: Milwaukee Convalescent Serum Center, Los Angeles Children's Hospital Convalescent Serum Center, Samuel Deutsch Convalescent Serum Center of the Michael Reese Hospital in Chicago, and the Philadelphia Serum Exchange of the Children's Hospital in that city. It is now the consensus (Hoyne *et al.* [1935], Hyland and Anderson [1937], Hamilton and Togasaki [1939], Fox and Hardgrove [1940]) that convalescent serum is fully as effective as antitoxin in reducing the toxic symptoms in scarlet fever and possibly more effective in preventing complications; in addition, if properly given (see below), sensitization or unfavorable reactions do not occur. Occasionally there is an urticaria-like eruption but not true serum sickness. No blood typing or matching is required.

Method of Administration—The serum should be given as early as possible, preferably within the first three days. Usually a single injection is sufficient.

if given early in uncomplicated cases, but when severe complications are present, the injections may be repeated at twelve to twenty four hour intervals. The Milwaukee Serum Center, in 1941, advises the following dosage

	Moderate	Severe
Infants	20 cc.	20-40 cc.
Children	20-40 "	60 "
Adults	40-80 "	80-100 "

Intramuscular therapy is satisfactory but the intravenous route is preferable because of the immediate distribution of serum. Warm the serum to body temperature in a water bath (over heating will coagulate the serum and make it unfit for use). Inject slowly. If using the intravenous route, the syringe should be absolutely chemically clean and sterilized by boiling in distilled water.

Immunotransfusion—Gordon (1933) tried the transfusion of whole unaltered blood from recently recovered patients which is believed to have value for its nutritive effect, its beneficial effect on the secondary anemia, its transfer of large numbers of phagocytic leukocytes and also for the passive immunity which it confers. No person was used as donor before the fifteenth day of the illness and he preferred that convalescence should not have exceeded three or four months as the other extreme. For infants and small children usually 100 to 150 cc was given, for older children about 300 cc, and for adults 500 cc. Sometimes 2 or 3 transfusions were given, much less often a larger number. From his experience in 246 cases Gordon felt that immunotransfusion has its most important indication in acute septic scarlet fever (so-called 'scarlatina anginosa' or 'scarlatina necroticans'), in the late septic complications of the ear, nose and paranasal sinuses, and in postscarlatinal bacterial endocarditis. The blood of several individuals can be mixed, indeed, this is perhaps advisable as the efficiency of some sera is greater than others irrespective of the severity of the attack through which the donor has passed. Hoyle *et al* (1935) used such transfusions in addition to convalescent serum in complicated cases seen in the late stages of the disease, and were satisfied that they thus increased the patient's chances of recovery. I have seen no other reports of large scale studies, but numerous physicians seem to have been favorably impressed by the method.

Sulfonamides—That sulfanilamide does not affect the toxic stage of the disease—that it does not lower the fever or shorten its course, or cause a diminution in the rash or an improvement in the sore throat—has now been firmly established by a large number of studies which I shall not utilize space to list here. It is likewise conceded to be exceedingly valuable in reducing mortality when employed in the treatment of serious complications. But the effect of its use from the beginning of an attack upon the incidence and severity of septic complications is another matter. The National Research Council Committee in its report to the Surgeon General, in 1941, apparently considers the value of the drug in averting complications is established, for it recommends that it be routinely employed in all cases for 'prophylaxis of septic complications'. Admittedly, the majority of reports indicates that precisely this will be accomplished, but my own feeling is that the last word

has not been said upon this subject and that perhaps by the time I come to revise this book again the majority opinion will have been reversed. The reasons are the following:

(a) A number of very carefully performed studies are in existence which do not show the alleged favorable effect—Peters and Havard (1937), Hogarth (1937), Schwenker and Waghelstein (1938), Wesselhoeft and Smith (1938), Peters *et al* (1939), French (1939), and Rascoff and Nussbaum (1940). The most completely controlled of these studies is that of French, who treated 340 cases at Ruchill Hospital in Glasgow, 170 with and 170 without sulfanilamide. The investigation was divided into two periods, the first comprising July and August and the second January, February, and March, thus avoiding unfair allocation of cases with regard to season. During these periods alternate cases were allotted to the two groups as they were admitted. The general medical treatment was the same in both groups and all patients who upon admission appeared to require antitoxin were given it, of the total lot, 79.1 per cent were given the antitoxin and it happened that they were precisely evenly distributed, 135 in the sulfonamide group and 134 in the control group. The drug was given in large doses for four weeks without a break and the patients were under French's personal clinical care throughout the entire period. "The results show that sulfanilamide had no significant effect upon the initial symptoms of scarlet fever or upon the kind, incidence or duration of later complications."

(b) It is not consistent with the history of the specific chemotherapeutic agents that any of them may be expected to be shown ultimately to be effective in a disease in which doubt of their effectiveness still persists after several years of world wide trial.

(c) If the attempt is to be made to prevent complications with this drug then it must be used for a full four-week period, just as French did in the above cited study, for it has long been known that with regard to complications there is a "second danger period" in the third and fourth weeks. Wesselhoeft (1941) does well, it seems to me, in pointing out that such a procedure will considerably increase the cost of medical care in scarlet fever, referring of course not to the purchase price of the drug but to the expert laboratory supervision which experience has taught is necessary when one is prescribing sizable dosage of a sulfonamide over an extended period of time. In short, routine sulfonamide therapy in scarlet fever is likely to convert a home treated into a hospital treated disease in private practice.

The study of Hoyne and Bailey (1937) indicated that when sulfanilamide is given during the fourth week of convalescence it cannot be trusted to reduce the number of carriers of hemolytic streptococci after the attack.

PROPHYLAXIS

Quarantine—The traditional rule for discharge from quarantine is that the desquamation shall be complete and that there shall be no suppurative discharges from any part of the body, moisture or discharge of any sort from the nose constitutes "discharge" though not obviously suppurative. However, it has long been recognized that the desquamating material is not infectious and that therefore the only purpose served by maintaining quarantine to the end of desquamation is to hold patients in isolation long enough for sup

purations to appear. Whether patients whose scarlet fever has been complicated are more dangerous to the community following release than others is at present still a controversial question. The law in many parts of the United States requires quarantine for a minimum of four weeks from date of report, but in some areas this has been modified to two weeks for adults and three weeks for children. Here in Milwaukee the period is three weeks if there are no infectious discharges or the patient is not still suffering from some other infectious complication in which discharge is not a feature, exposed contacts are kept in quarantine for one week.

A number of men are in opposition to present quarantine regulations and feel that when a child recovers as rapidly as is frequently the case nowadays there is no reason to hold him so long. Musser (1941) goes so far as to call the present regulations ridiculous and I gather the impression from his paper that he would be satisfied to discharge any patient in a week if he were completely recovered in that time.

Convalescent Serum—There is such agreement regarding the efficacy of human scarlet fever convalescent serum in preventing or greatly modifying the disease that it will perhaps suffice for me merely to cite our own experience here in Milwaukee. Doctor Maurice Hardgrove, Director of the Milwaukee Serum Center reported in 1938 that of 1061 individuals exposed to scarlet fever and given protective convalescent serum only 20 (1.83 per cent) developed the disease within fourteen days while the office of the City Health Commissioner stated that 13.5 per cent of the unprotected contacts in the city were developing the disease within this time during the same period. The Center recommends as prophylactic dosage 10 cc for infants and young children and 20 cc for older children and adults. The injection is given intramuscularly and should be repeated every ten to fourteen days in patients having successive exposures. Neither sensitization nor serious reactions need be feared but very mild reactions occurred in about 1 per cent of Hardgrove's cases: slight transient elevations in temperature, occasional urticaria and joint pains lasting but a few days.

Fresh Parental Serum—The method of Barenberg (described in Measles) is an interesting approach from the standpoint of contagious diseases in a hospital.

Immunization with Toxin—This method comprises the use of the Dick intracutaneous test for susceptibility and the subsequent active immunization of positive individuals by the injection of multiple doses of the Dick toxin.

The Dick Test—Inject 1 skin test dose of Scarlet Fever Streptococcus Toxin (0.1 cc of the Dick test material as marketed) intracutaneously in the forearm after thoroughly cleansing the area with green soap. Inspect after twenty-two to twenty-four hours. An area of redness and slight infiltration $\frac{1}{2}$ inch or more in diameter indicates susceptibility. Positive reactions fade rapidly and have usually disappeared in forty-eight to seventy-two hours but reactions which have entirely faded at the end of twenty-four hours are regarded as negative. Because of the extreme sensitiveness of the test, the Dicks advise sterilization of the syringe in distilled water and rinsing of syringe and needle with the test solution before making the injection. The statement is made in the 1941 N.A.R. that the toxin diluted for use will retain its potency for at least two months at room temperature.

Immunization—Five doses of the immunizing toxin are given subcutaneously in alternate arms at weekly intervals. As marketed, these doses contain

First injection 250 skin test doses	Third injection on 10 000 skin test doses
Second injection on 2500 skin test doses	Fourth injection 90 000 skin test doses
Fifth injection 100 000 to 120 000 (as noted on the vial) skin test doses	

Reactions—Reactions may occur after any of the doses but are most common after the third and fourth they usually appear in six hours and in most instances have disappeared again in twenty four hours. The following are the symptoms: nausea, vomiting, fever, scarlatinal rash, sore throat, joint pains, painful cellulitis at the site of injection, occasionally edema and rarely anasarca. Even the staunchest advocates of this method warn against its use in any child in whom one has the least reason to believe from suggestive symptoms, that scarlet fever infection is already established and that if a Dick positive individual has been exposed to scarlet fever one should observe him for two or three days before starting immunization and that no immunization injection should be made in any individual (exposed or not) until forty eight hours have elapsed after reading the positive Dick test. It is also considered wise not to immunize children with chorea, rheumatism, heart disease, asthma, eczema and the other allergic ailments.

In recent years an attempt was made (Anderson 1938) to introduce a less toxic antigen comparable to the diphtheria 'toxoid' but for various reasons the use of such material did not become general. The most recent attempts at modification which will bear watching are the intracutaneous method (Kern *et al.* [1938] and Fisher and Van Gelder [1941]) and the oral method (Dick and Dick 1949).

Appearance and Duration of Immunity—As determined by conversion of a Dick 'positive' to 'negative' immunity may be demonstrated two weeks after the last injection. Some observers believe that temporary immunity of variable duration is conferred upon the majority of children; the Dicks say that probably 90 per cent of those properly injected are permanently immunized.

Status of the Method—In recent years disagreements with the theoretical bases of this method of immunization and objections to its further trial have greatly increased in number and force. The following are the chief points made by those who question the value of present methods of Dick testing and immunizing (Bauer, Collis, Earle, Friedman *et al.*, Hobson, Hooker and Follensby, Peterman, Peacock *et al.*, Gordon, Maxcy Hill).

1 The Dick toxin, since it does not represent all the strains of streptococci associated with scarlet fever, and since equally toxigenic strains of streptococci can be recovered from diseases other than scarlet fever, cannot form a valid basis for either a theoretically justifiable 'test' or immunization.

2 Practical justification of the test has failed to be established since scarlet fever frequently in a malignant form has developed in Dick test-negative individuals. Furthermore a large proportion of positive reactions is obtained in individuals known to have had a bona fide attack of scarlet fever.

3 Most bacteriologists insist that it is not possible to induce complete active immunity against any streptococcus.

4 The Dick test is much too difficult to read to be of practical use

5 Attempted immunization prevents, only the appearance of the rash thus robbing the physician of the most valuable sign of scarlet fever and preventing the isolation of these patients, who have scarlet fever without rash

6 Even granting that "immunization" really immunizes, only the principal protagonists of the method claim that the immunity is a lasting one

7 The reactions to immunization are often so severe that the patient is more ill than he would be with the naturally acquired disease

Sulfonamides—Jewell (1940) has published a note on the successful employment of sulfanilamide in small doses as a prophylactic agent. Wesselhoef (1941) trenchantly remarks that spectacular results were also claimed sixty years ago for belladonna in this same role, references to the subject at that time filling two columns of the *Surgeon General's Catalogue*. The control method of investigation finally eliminated belladonna from consideration and we can only await the application of the method to sulfanilamide to learn if its fate is to be any more fortunate

SEPSIS

(Septicemia)

Following the example of Herrick and the frequent Continental usage, I employ the term 'sepsis' for the description of a syndrome which it is more usual to designate 'septicemia' in the United States. This departure is made for the reason that the term 'septicemia' places too great stress upon the presence of the causative organism in the blood stream and tends to foster the misconception that this disease entity is characterized by a state of affairs in which large numbers of the organisms are constantly floating about and multiplying in the circulating fluids of the body. To be sure, eruption of the causative micro-organism into the blood stream and perhaps a succession of such eruptions, is a *sine qua non* for the development of sepsis but the mere presence therein of these organisms is not in itself enough to justify the diagnosis—as witness typhoid fever, in which there is a more or less persistent bacteremia despite which we do not refer to the case as one of septicemia. From first to last sepsis is a clinically recognizable entity, which has at some time in its course the laboratory-demonstrable feature of organisms in the blood stream, but as Churebman so well pointed out, it is not the fact of their presence there that is of importance, but rather that they have come from somewhere and are going somewhere else. The really serious fact therefore is that a barrier has given way and enabled a local disease to become general.

Most cases of sepsis follow a surgical operation, an abortion or child birth, an acute or chronic sinus infection or an infection of the same sort in the male genitals or the female pelvis, a sore throat, otitis media, a boil or carbuncle, a compound fracture, or a traumatic injury often of apparently trivial nature, in a minority of cases the original nidus cannot be located

About two thirds of the cases are due to the streptococcus, principally the beta hemolytic streptococcus, with probably half this number caused by *Staphylococcus aureus*, and the remainder by *Acisseria intracellularis* (meningococcus), *Clostridium welchii* (gas bacillus), *Hemophilus influenzae* (influenza bacillus), *Diplococcus pneumoniae* (pneumococcus), *Escherichia coli* (colon bacillus), and in quite rare instances *Listerella monocytogenes*, *Salmonella suispestifer*, *Bacteroides funduliformis* and a few others. The onset is usually sudden, with chill and high rise of temperature (the type of which varies somewhat with the organism involved) and rapid pulse and respiration, sweats, frequently gastro intestinal symptoms, leukocytosis, multiform skin lesions, and a nervous involvement which varies between the extremes of wild delirium and coma. What metastatic involvements are to supervene cannot be predicted in the beginning, meningitis, endocarditis, suppurative arthritis, and embolic phenomena are among those that most frequently occur. Some patients die very quickly from an overwhelming toxemia, others linger only to succumb after several weeks or even months. In the days before the advent of the sulfonamides, Tileston placed the general mortality at 60 to 80 per cent, Herrick at 70 to 90 per cent, the latter stated that if one eliminated cases with meningitis, endocarditis, general peritonitis, or pyelophlebitis (all of which were almost uniformly fatal) the average death rate was only 50 per cent.

It was principally sepsis, of course, that made the hospitals of old the shambles that they were. Even as recently as the eighteenth century physicians declined hospital service "as equivalent to a sentence of death." Reforms followed the independent reports, in 1777 to 1789, of Tenon with regard to the deplorable state of affairs in the Hôtel Dieu in Paris and John Howard on numerous institutions on the Continent. However, real cleanliness only came into effect after Florence Nightingale began her labors in 1854. Lister, in 1867, inaugurated the era of surgical antisepsis which finally led to the aseptic technic. And now at long last the sulfonamides have effected a considerable change in the results attainable in treating the disease.

THERAPY

Sulfonamides—The undoubted efficacy of this group of drugs in sepsis is not likely ever to be proved in a controlled series in which alternate cases are handled with and without the drug as they come, the reason being of course that justification for withholding so important an agent in a malady so fatal as this could not be found. However, a near approach to such a study has been published by Herrell and Brown (1941) of the Mayo Clinic, who reviewed the results in a series of cases treated in a two year period after the use of the sulfonamides became general with a nonsulfonamide series treated in the preceding two years. Confining themselves to cases caused only by a hemolytic streptococcus, *Streptococcus viridans* (but not including subacute bacterial endocarditis), *Staphylococcus aureus*, the pneumococcus and the colon bacillus, because the numbers of other cases were too small to be of significance, they had 103 treated cases to compare with 171 untreated cases. It was concluded that the recovery rate was about doubled in general but that this does not represent the best that can be attained for the reason that in the cases most frequently encountered, namely

those caused by hemolytic streptococci and *Staphylococcus aureus*, the results were uniformly much better than this. They found also that the three factors of greatest prognostic significance—the age of the patient, the colony count on initial blood culture and the maximal leukocyte count—prior to the advent of sulfonamide therapy had lost this significance as indicated in the following: (a) Among patients more than fifty years of age, in whom mortality was previously highest, the recovery rate was increased sixfold, (b) Approximately as many patients recovered whether the initial colony count was high or low, (c) Maximal leukocyte count did not substantially affect the recovery rate. A fact which adds to the significance of this report of Herrell and Brown is that it dealt with patients treated only with sulfanilamide and sulfapyridine and toward the end of the study some sulfamethylthiazole—but not sulfathiazole or sulfadiazine for these were not yet in clinical use.

Undoubtedly today in any case of sepsis prompt and thorough employment of the sulfonamides is imperatively the therapy of choice. This is true whether the organism be a streptococcus, staphylococcus, meningococcus, pneumococcus, colon bacillus, influenza bacillus, gas bacillus or so rare an invader as for example *Bacteroides funduliformis* or *Micrococcus tetragenus*. There is a chapter on Sulfonamide Toxicity at the end of the book.

Sulfanilamide—In the middle of 1941, Barker, expressing the feeling of Long and the Johns Hopkins group at that time, stated that sulfanilamide is still the preferred drug in beta hemolytic streptococcus infections including sepsis as defined in this present article: streptococcal sore throat, cellulitis, lymphangitis and lymphadenitis, erysipelas, scarlet fever, beta-streptococcal empyema and beta streptococcal meningitis. It was also considered at that time still the preferred drug in gas bacillus infections.

In order to obtain the desired blood level of 10 to 15 mg. per 100 cc. as rapidly as possible in severe cases it is customary to follow the dosage plan of Long (1940) who gives an initial oral dose of 0.1 Gm. per kilogram of body weight (1½ grains per 2½ pounds) subsequently an amount the same as the above is divided into 6 parts and 1 part is given every four hours day and night until seven days of normal temperature have elapsed. In mild and moderately severe infections in which it is felt necessary to establish levels of only 5 to 10 mg. per 100 cc., the initial large dose is omitted but the same amount as above is given every four hours day and night until five days of normal temperature have elapsed. Since hemolytic streptococcal otitis media, mastoiditis or osteomyelitis are infections involving bone, it is believed that in these cases sulfanilamide medication should continue for at least ten days after clinical cure has been effected. The drug may be administered to infants and young children by crushing the tablets in a small quantity of water and feeding with a spoon, indeed there may be an advantage in administering the drug in somewhat the same fashion to adults as absorption of the powder is likely to be more rapid than of the tablets which may not dissolve at once in the stomach. Sulfanilamide permeates the entire body including passage over into the cerebrospinal fluid therefore intrathecal administration is not necessary. In the relatively rare instances in which vomiting precludes retention of the drug given by mouth, or if there is reason to believe that absorption is not taking place with sufficient rapidity or regularity, sulfanilamide may be given by hypodermoclysis. In these cases it is the usual practice to

bring a measured quantity of physiologic saline solution (or sixth molar sodium racemic lactate or lactate Ringer solution) to a boil, cut off the flame add enough crystalline sulfanilamide to make a 1 per cent solution, and shake gently until the drug dissolves. The solution should be prepared each day be kept at room temperature as settling out of the drug will occur in the refrigerator and be administered at body temperature. Sulfanilamide in 1 per cent solution in saline may actually be autoclaved at 15 pounds' pressure for five minutes without causing decomposition but this method is rarely employed. Long says that the initial hypodermoclysis in severe cases should contain an amount of the drug equivalent to 0.1 Gm. per kilogram of body weight ($1\frac{1}{2}$ grains per 2.2 lbs.) and that subsequent hypodermoclyses at six to eight hour intervals should contain one half to three fourths this amount. Oral administration should be resorted to as soon as possible. The sulfanilamide solution is not to be given intravenously or intramuscularly. *Neoprontosil* which is commercially available in ampules may be given subcutaneously every four hours if desired but it should be understood that none of the claims for the superiority of this drug over sulfanilamide have been established. The studies of Turell *et al* (1940) and Strauss *et al* (1941) indicate fairly good absorption of sulfanilamide from the rectum, Wood (1941) follows the practice of keeping on hand a solution of sulfanilamide saturated at room temperature which amounts to approximately 4 grains to the ounce (0.25 Gm. per 30 cc.), and then adds the desired quantity of this to a dextrose saline solution and administers four hourly as a retention enema. None of the other sulfonamides are well absorbed from the rectum.

Long (1940) says that he has known very great difficulty to be experienced at times in maintaining the necessary concentration of drug in the blood stream when large quantities of fluid were being administered. He holds that when patients are being given sulfanilamide it is rarely necessary to force fluids beyond 3500 cc. per day.

Sulfapyridine—In meningitis caused by the pneumococcus the influenza bacillus *Streptococcus viridans* and the salmonella organisms as well as in bacteroides septicemia, this drug has proved definitely superior to sulfanilamide. The dosage scheme of Rhoads *et al* (1940) is usually followed. In adults the sodium salt of sulfapyridine in doses of 4 to 6 Gm. (1 to $1\frac{1}{2}$ drachms) in 5 per cent solution is given intravenously, repeating every twelve hours until a blood level of 10 to preferably 20 mg. per 100 cc. is reached usually thereafter large doses up to 2 Gm. (30 grains) every four hours day and night are required by mouth to maintain this level for the first few days though slightly smaller doses at the same intervals may suffice. For children the dosage is 1 to $1\frac{1}{2}$ grains per pound body weight (0.06 to 0.1 Gm. per 450 Gm.) for each twenty four hours the dose being administered in equal parts every four hours after an initial dose equaling one-half the calculated day's dosage. Administration is begun by mouth as soon as it seems desirable and safe. Sulfapyridine administration should continue until the temperature has been normal for several days and the spinal fluid and blood cultures are normal.

Sulfathiazole—In staphylococcal sepsis the superiority of this drug to either sulfanilamide or sulfapyridine is definitely established, Spink and Hilger (1941) give it the preference also in *Streptococcus viridans* infections.

In cases of staphylococcic meningitis, sulfathiazole has not done well because it does not readily diffuse into the spinal fluid. However, Sadusk and Nielsen (1941) have reported the interesting intraspinal administration in 1 case with recovery. Oral administration, which had produced a satisfactory blood but not spinal fluid level, was supplemented by twice daily intraspinal injections of 40 cc of 0.5 per cent sodium sulfathiazole in physiologic saline solution, following the drainage of an equivalent amount of spinal fluid each time, the patient was an adult.

In staphylococcic sepsis, Spink *et al* (1941), who have reported the treatment of 15 consecutive patients, give an initial oral dose of 60 grains (4 Gm) and then 15 grains (1 Gm) every four hours. In all of these cases the blood was sterilized and all the patients recovered.

Sulfadiazine—In his preliminary review of this new drug, Long (1941) says he believes it has definite value in hemolytic streptococcus and staphylococcus infections. The dosage scheme in average instances for adults is an initial oral dose of 60 grains (4 Gm) to be followed by 15 grains (1 Gm) every four hours for 6 doses, thereafter 15 grains are given every six hours until the patient's temperature has been normal for seventy-two hours. Finland *et al* (1941) report 8 patients with erysipelas who responded quickly and fully to sulfadiazine. This drug passes over into the spinal fluid as well as do sulfanilamide and sulfapyridine.

Promin and Sulfabenamide—These drugs are having interesting clinical trials but I do not feel warranted as yet in including a discussion of them here.

Elimination of Foci—It is certainly the consensus that employment of the sulfonamides should not preclude attempts to halt the influx of organisms into the blood stream by eliminating the primary or secondary foci. Sometimes this is relatively easy, as in the case of carbuncle, or sinus thrombosis following a mastoid operation, or empyema, but the inaccessibility of the focus, or the gravity of the patient's condition, oftentimes makes radical interference impossible.

In puerperal sepsis, especially if it follows incomplete abortion, some practitioners believe that an attempt should be made to evacuate remnants of the placenta from the uterus, if this can be done without anesthetic, following this an antiseptic douche should be used (Hirst recommends tincture of iodine 2 drachms, 95 per cent alcohol 8 ounces, sterile water to make 2 quarts, Hobbs introduces a catheter into the uterus in the morning and irrigates with 100 cc of warm glycerin every hour for from three to six hours, then removes the catheter), but if the temperature continues high, or drops and soon again rises high, no further manipulations should be performed and even the douche or glycerin irrigation should be discontinued. Perhaps the majority of obstetricians, however, disagree with this plan of treatment and prefer a radical policy of "hands off" from the very beginning in all cases, the only interference they employ is the draining of accessible pelvic pus collections as soon as they develop.

Whether, in a given case of nonpuerperal peritonitis, the attempt is to be made to remove the focus of infection, or reliance is to be placed in the Ochsner type of treatment comprising complete rest for both body and bowel (absolutely the minimum amount of disturbance of the patient, nothing whatsoever by mouth, hypodermoclysis, nutrient enemas, and opium to check peristalsis and relieve pain)—these are nice points in surgical practice

which of course we cannot dwell upon here. It is to be noted, however, that recent writers (Botsford and Lanman, 1939, Ladd *et al.*, 1939) have stressed the importance of early drainage in primary peritonitis in infancy and childhood, in one of the cases reported the patient was receiving sulfanilamide therapy for a streptococcic sore throat, and had had adequate blood levels of the drug for several days, when peritonitis developed.

Placing the patient in the well known Fowler position is of great advantage in pelvic cases, walling off of the local process is thus facilitated and its spread to other parts of the peritoneal cavity, as well as the access of organisms and toxins to the general circulation, is made much more difficult. But the fact must not be overlooked that too long maintained interference with venous return from the pelvis is thought (Mensing) to predispose to phlebitis and the dangers of pulmonary embolism. Likewise, if the blood pressure falls very low, the upright position unquestionably furthers cerebral anemia.

Antiserums—Antistreptococcus serum has been before the profession since 1895 and is still waging a fight to hold what little good opinion it may have gained, lack of evidence of its therapeutic worth in sepsis prevents its acceptance by the Council on Pharmacy and Chemistry of the American Medical Association. There is certainly no convincing report of any greater success with scarlet fever antiserum. Staphylococcus antiserum likewise has practically nothing to its credit, though it will certainly be worthwhile to watch the rabbit serum containing a high titer of precipitins for staphylococcic polysaccharides with which Julianelle (1939) has been experimenting. Neal *et al.* (1940) have reported the use of specific antisera in most of 30 cases of pneumococcic meningitis and 20 cases of influenza bacillus meningitis with 10 recoveries in the first group and 14 in the second, but they attributed these fine results to the sulfonamides which were also employed.

Specific Antiserum Plus Serum Transfusion (Cadham)—Cadham, of Winnipeg, a few years ago developed an ingenious method of attempting to supply specific antibodies in sepsis. He kept a colony of rabbits immunized against numerous strains of streptococci and staphylococci recovered from septic patients. Then, when a patient with sepsis was to be treated a vaccine was prepared from the causative organism as rapidly as possible and inoculated into several of the rabbits, on the next day, blood was drawn from one of the rabbits and the serum of same was injected subcutaneously or intramuscularly into the patient, the several rabbits were used in this way in rotation on successive days. At the same time as the injection was made into the patient he was transfused with the serum from 60 to 100 cc. of compatible blood. Cadham believed that with this procedure both immune bodies and human complement were supplied simultaneously to the patient. His results were good and were reported in a conservative tone, but I have heard nothing recently of the matter.

Bacteriophage—This agent has had a long time in which to prove its case and hasn't done it yet. The latest report is that of Longacre *et al.* (1940), who felt that bacteriophage was responsible for the relatively low mortality of 47.2 per cent in their 36 cases of staphylococcic sepsis. I suppose this will stimulate a few others to give the thing a trial again.

Foreign Protein Therapy.—Since 1914 the nonspecific foreign proteins have been much used in the treatment of infectious diseases but we

have no extensive statistical studies of their efficacy. Typhoid vaccine intravenously, or milk intramuscularly will probably accomplish all that can be expected from any of these proteins. The milk is boiled for ten minutes, cooled to body temperature, and 5 to 10 cc injected into the gluteal region. From 25 000 000 to 100,000,000 of the typhoid bacilli in the ordinary vaccine are slowly introduced into a vein. It is thought that the good results follow upon the more or less violent reactions which succeed these injections. Such measures are very rarely resorted to now that we have the sulfonamides.

Induced Abscess—The production of a local abscess in the hope of thus stimulating general production of antibodies was a practice regularly followed by a few practitioners prior to the introduction of the sulfonamides. I imagine it is little resorted to nowadays. The procedure is to inject about 10 minims (0.6 cc) of the oil of turpentine into one of the buttocks and then drain the abscess when it is fully formed.

Immunotransfusion—Simple blood transfusion is often resorted to in sepsis, occasionally with some measure of success. In the cases of pronounced anemia, which is many times a part of the picture in streptococcal cases, it would seem to be especially indicated. "Immunotransfusion" indicates the use of blood from a donor in whom the formation of nonspecific antibodies has been increased by the intravenous injection of killed typhoid bacilli, a method suggested by Wright some years ago. A suitable donor, selected by typing, cross agglutination and serology, is put to bed and given 50 000 000 bacilli intravenously (0.05 cc of commercial typhoid paratyphoid vaccine). Within an hour his symptoms set in (if not, 25 000 000 more bacilli may be given): headache, malaise, chills and fever, occasionally nausea, vomiting and diarrhea. The transfusion is performed about eight hours after injecting the vaccine at which time the most acute symptoms have usually subsided. The donor returns to normal within twenty-four hours, but he should not be used a second time in less than two weeks. The blood, if it is to be used for frequent small transfusions, may be safely kept on ice (citrated of course) for forty-eight hours. It is usual to give 300 to 500 cc to the patient every twenty-four to forty-eight hours, but in severe, rapidly progressing infections transfusions of 100 to 200 cc at six to twelve hours may be superior. The patient may experience a sharp chill and rise in temperature when the transfusion is given, but more serious reactions have not been reported. There has certainly not been much enthusiasm over the effect of such immunotransfusions on the mortality rate in sepsis, but it may be possible to improve the methods. One modification, which requires considerable time, is to make the blood "specific" by inoculating a donor with 4 weekly injections of a vaccine prepared from the streptococcus isolated from the patient's blood, doses increasing from 50 000 000 to 250 000 000 killed organisms. Crocker *et al* (1933) felt that the proper time for transfusions to the patient can best be determined when a shift to the left in his Schilling hemogram indicates increasing intoxication. Dyson and Miller (1934) believed that in selecting donors those giving the least reaction to the patient's vaccine should be used on the assumption that they possess the highest natural immunity. They make two other suggestions: (1) that the blood be kept at 101.5° F and be injected at this temperature, and (2) that the specifically immunized donor be given a dose of pentnucleotide four to eight hours before drawing

bis blood, this with the idea of increasing the outpouring of specific antibodies Lyons (1935) determines the relative amounts of specific antibodies of potential donors by a method too technical to present here

Supportive Care—Unless it is necessary to rest the bowel the diet should be as nutritious and full as possible. When nutrition is not being maintained because of inability to retain food in the stomach the nutritive enema (see Index) should be given consideration. Diluted orange juice or lemonade are pleasing forms in which to administer nourishing fluids by mouth. When the patient is vomiting it is often advisable to discontinue the attempt to supply food and fluid by mouth and to resort to the intravenous administration of dextrose, either occasionally or by the continuous drip method (venoclysis). If the dextrose solution is prepared with physiologic saline or preferably Locke's solution, the loss of chlorides occurring in excessive vomiting is combated. The dextrose is also protective against acidosis. Hypodermoclysis of physiologic saline solution will of course supply fluid and chloride but no nutriment. If the attempt is not being made to have one of the sulfonamides retained when administered by mouth the introduction of a Levin duodenal tube for continuous drainage (with suction if necessary) of the stomach may be helpful.

SMALLPOX

'Since my Lady Mary Wortley Montagu brought home the custom of inoculation from Turkey (a perilous practice many deem it and only a useless rushing into the jaws of danger) I think the severity of the smallpox (that dreadful scourge of the world) has somewhat been abated in our part of it and remember in my time hundreds of the young and beautiful who have been carried to the grave or have only risen from their pillows frightfully scarred and disfigured by this malady. Many a sweet face hath left its roses on the bed on which this dreadful and withering blight has laid them. In my early days this pestilence would enter a village and destroy half its inhabitants: at its approach it may well be imagined not only that the beautiful but the strongest were alarmed and those fled who could. One day in the year 1674 (I have good reason to remember it) Doctor Tusser ran into Castlenode House with a face of consternation saying that the malady had made its appearance at the blacksmith's house in the village and that one of the maids there was down in the smallpox.'

—W. M. Thackeray *'The History of Henry Esmond'*

Smallpox has doubtless existed since the earliest times in China, India, Africa and the Mediterranean littoral, though there is considerable doubt whether it was described by the Greeks or even the early Romans. Greenwood says that it entered Europe with the Saracens; it did not reach England until the tenth century. Cortez brought it to the western hemisphere (Mexico) shortly after the discovery of the New World. The first medical publication in North America dealt with smallpox (Thacher's "Brief Rule to Guide etc.," Boston, 1677). According to Russell (1940) the disease did not reach Hawaii until 1853 when it promptly carried off 8 per cent of the population. The malignant "classical" form (variola) still holds ravaging sway in the hinterland of the less enlightened countries, with a mortality of about 25 per cent, and in well vaccinated lands, such as certain of the continental

European countries, the rare outbreaks are of this type. In some of the "enlightened" lands where the vaccination rate is very low, such as the United States, England and a few more, smallpox has a quite high incidence, but for reasons not as yet understood, the disease is very mild in form—the so-called "varioid," with a mortality rate not over 1 per cent. But the present mildness of the disease in these countries does not insure that the old malignant smallpox cannot easily establish itself again, indeed this happens now and then when smuggled labor from one of the endemic foci of classical smallpox is brought into a land in which the prevailing form is mild—for example, Mexican laborers have started several such outbreaks in the United States. The disease known in various parts of the world as *alastrum*, *amaas*, and *parasmallpox* is considered to be probably identical with mild smallpox, but students of the matter are still far from certain that it is so.

The black race is much more susceptible than the white. The disease is caused by an unidentified virus and is contagious by contact during any time that there are symptoms, it is probably also air borne to some extent, at least such dissemination has not been disproved. It is more frequent during the colder months of the year. The average period of incubation is from ten to twelve days, but it may be from five to twenty-one days.

It is not in order here to describe the various types of smallpox, such as the confluent, the purpuric and the hemorrhagic, the following is a brief description of the classical type of attack. Onset is usually abrupt with a chill or chilliness, headache and severe backache, rapid and high rise in temperature and accompanying rise in pulse and respiratory rates, generalized body pains and nausea, and many times persistent and violent vomiting. Menstrual flow often appears out of its due order and abortion is frequent. About three days after the onset of the disease a macular eruption appears (on the face and wrists first) which soon becomes papular, and in another three days this has become vesicular, some of the vesicles become umbilicated and multilocular. About the ninth day of the disease the pocks will have become pustular. Schamberg has estimated that in a case of moderate severity there may be as much as 5 quarts of pus contained in the pocks all over the body. At this stage the patient is often very odorous. Lesions, which stop short of vesiculation, are frequent on the mucous membrane of the mouth, nose and tongue, usually also there is enough involvement of the pharynx and larynx to make for extreme discomfort and hoarseness. At the appearance of the eruption the fever and other symptoms usually sharply subside, but this is not invariable, at this time also the patient may manifest signs of cerebral disturbance, which is usually more truly a dementia than a delirium. Following the afebrile period there is a second rise in temperature which coincides with the pustular stage of the eruption. This second period of fever terminates with the beginning of desiccation, about the twelfth day of the eruption, but may continue for a long time if the case has become one of secondary sepsis. One attack usually confers immunity for life but rare second and even third attacks are on record.

THERAPY

McCammon's (1939) use of sulfanilamide in a small family outbreak indicates that a thorough trial of this drug is warranted when the diagnosis is

presumptively made before the appearance of the pocks. Four of his cases were treated with the drug and 3 without—the untreated patients all developed the typical eruption, but in 3 of the treated patients there was only an evanescent macular eruption which rapidly disappeared and in the remaining patient only three pustules developed. McCammon says those who received sulfanilamide were back at work about a week sooner than those who did not. A nutritious diet and plenty of fluids are indicated as in all of the infectious diseases. In the beginning it is desirable to relieve the severe pains by the use of such remedies as acetylsalicylic acid, 10 grains (0.6 Gm.) every three or four hours, phenacetin, in the same dose and at the same intervals, or amidopyrine in a dose of 5 grains (0.3 Gm.) (see under Agranulocytosis for toxic action of this drug). Sometimes these milder agents will not suffice, and morphine or dilaudid must be given. The vomiting is perhaps best controlled by gastric lavage with 1 per cent sodium bicarbonate solution. Cowie states that severe vomiting is quite regularly controlled by the slow intravenous injection of dextrose solution.

The severe itching that often occurs is much relieved by the following lotion, which has the objection, however, that it dries into a thin crust that may aggravate the condition unless it is frequently washed off with olive oil, not with water.

R Phenol.	3ss	2 0
Prepared calamine	5 iiss	10 0
Zinc oxide ..	5 iiss	10 0
Glycerin	ꝑss	2.4
Solution of calcium hydroxide to make .	5 iv	120 0

Twenty per cent argyrol solution should be dropped into the eyes twice daily from the beginning, and one should be especially attentive to the possibility of scarring from conjunctival lesions if the face is so much swollen as to close the eyes.

It would seem that all measures directed toward limiting the amount of scarring are unavailing (unless McCammon's observations, previously referred to, are confirmed). If scratching were the chief factor, then it would seem that children should be the most afflicted in this regard; the fact is, however, that the cosmetic result is very much better in children than in adults. Scratching is of course to be resisted as much as possible for it certainly increases the liability to secondary infection.

Removal of Scars.—The use of trichloroacetic acid is said to be sometimes successful in removing smallpox scars (Wise, 1920). Fisher (1938) reported the removal of an accidental (autovaccination) scar by the use of blistering doses of ultraviolet rays.

Preventive Vaccination with Standard Calf Lymph.—It is said that the Chinese have for many centuries practiced a crude kind of vaccination by thrusting human smallpox scabs up the nose. The Turks had refined upon this somewhat in that they introduced some of the pus from such a scab into a small incised wound of the arm; after an incubation period of a week or so the patient experienced a mild attack of the disease and was then immune. This was the practice which Lady Montagu brought home to England in 1727, where, after some preliminary opposition, it was much used until supplanted by the Jenner method; it also had considerable vogue in the American Colonies

—Krafft says that general inoculation of the army occurred during the Revolution. Schamberg says that the custom never enjoyed much popularity on the Continent. By all accounts these induced cases were by no means invariably mild. Jenner in England conferred upon the world the great boon of vaccination with the virus of cowpox in 1798.

In what follows I have drawn upon authoritative sources to supply answers to the chief annoying questions which arise in connection with present day vaccination.

Method — The site of vaccination should be thoroughly washed with acetone. Other antiseptics may destroy the virus. A drop of virus is placed in the center of the cleansed area. Holding a small sterile needle at an angle of 20 degrees from the skin surface the point of the needle is pressed into the skin through the drop about ten times. Obviously these pressure points should be in the same locality. No blood or serum should be drawn. The excess of virus is now wiped off with a piece of sterile gauze. There is some difference of opinion as to the advisability of putting a dressing over the inoculation. It is permissible to use no dressing. Certainly tight constricting bandages and shields should be strictly avoided. I always put one thickness of sterile gauze over the point of inoculation very loosely with a piece of tape. The mother is told to remove this next morning and put nothing more on it until the pustule appears. She is then told to place a similar piece of gauze on the pustule and to change it daily unless the pustule breaks and sticks to the gauze. If this happens the gauze is not removed. No tub bath is given the child from the time the pustule appears until the scab is on firmly. The mother is warned that a papule usually appears on the third to fifth day. In another day this becomes a vesicle and the next day a pustule with a swollen red area about it. At about the sixth day there is frequently some fever and loss of appetite. Mothers are told to report one week after vaccination for inspection and further instructions. (Sanford 1936)

Choice of Sites — Boys: over insertion of deltoid muscle on left arm. Girls: outer aspect of left thigh, two thirds of the way from knee to hip. It is worth noting that leg vaccinations are more likely to cause large scars than arm vaccinations and that primary leg vaccination in adults may be accompanied by purplish discoloration and cause temporary disability.

What Is a Successful 'Take'? — 1 Redness passing in eight to seventy two hours accompanied by slight elevation of the skin and perhaps itching indicates immunity at the time of vaccination. 2 A greater degree of this lasting three to seven days indicates there was only partial immunity. 3 With the typical full take indicating no immunity at the time the red areola reaches its broadest diameter in eight to fourteen days after vaccination and there is a turbid whitish vesicle which may or may not become a pustule before it dries and promptly heals. All three of these reactions are 'takes' because they indicated the degree of immunity and raised it again to maximum. Leake (U.S.P.H.S.) says that all other results indicate deficient vaccine if the technique was proper and the individual in good health.

Complications — (1) Excessive swelling, abscess formation and lymphatic enlargement indicate secondary infection. Cleanse the pustule with ether and paint with mercurochrome or gentian violet or metapben solution. Abscesses to be treated surgically with wet dressings. (2) Generalized vaccinia rare. Pustules around lesion or scattered papules and vesicles over body. Usually

only slight fever and prostration Prognosis excellent and recovery rapid (3) Autovaccination, caused by failure to wipe off excess of vaccine and the child's fingers carry it to other parts of the body or child scratches the uncovered pustule New pustules will be similar to original and are cause for no concern unless involving eyelid or cornea—which calls for ophthalmologic consultation at once (4) The British statistical study (1931), which may still be accepted as a reliable gauge of conditions obtaining throughout the western world, reveals that for each million persons vaccinated for the first time there are nineteen disorders of the nervous system, with six or seven deaths, and for each million persons revaccinated there is one such disorder, with a fatal issue Clearly, there is no cause for anxiety here Since the great majority of the cases are in children primarily vaccinated between the ages of three and thirteen, the well established precept of vaccinating in early infancy is roundly confirmed Jorge's (1932) study of these postvaccinal nervous disorders is most exhaustive

How Long to Continue Trying If No "Take" Is Obtained?—Failure to obtain one of the three kinds of reaction described above under "successful 'take,'" does not indicate immunity but only unsuccessful vaccination Repeat at two week intervals until a 'take' is had—there is a record of thirteen attempts before success was attained It is likely that many failures to obtain a 'take' are due to ignorance of the fact that merely placing the vaccine in the refrigerator on receipt is not sufficient precaution against loss of potency, it should be placed in a container in constant contact with ice (the glycerin in the vaccine prevents freezing), or in the electric refrigerator in an ice-cube compartment

Best Time of Year—Hot months predispose to infection because of perspiration and scratching in winter and early spring there are the respiratory infections which unintelligent parents may charge against the vaccination This leaves late spring and fall as the ideal seasons—but this matter is not of much importance

Contraindications—Women may be vaccinated at any time during pregnancy without fear of obstetrical complications, but successful vaccination of the mother does not convey specific immunity to the infant It is best not to vaccinate during menstruation Eczema, impetigo, furunculosis or other "open" skin diseases should cause postponement unless there is an epidemic, likewise gastro intestinal upsets or malnutrition Acute infectious diseases may cause delayed or atypical 'take' but are not in themselves contraindications in case of possible exposure Lymphomatous diseases such as leukemia and Hodgkin's disease may be made worse In adult pulmonary tuberculosis vaccination apparently may be performed with little risk if exposure necessitates, but in tuberculous children, and in bone tuberculosis at any age, one should be very cautious as some unfortunate things have been reported (J.A.M.A., 102:233, 1934) The diabetic, with his easy infection by pyogenic bacteria, should perhaps be vaccinated only during an epidemic Vaccination is not contraindicated in asthmatics or other allergies but such individuals may have more pronounced reactions, both local and constitutional An asthmatic attack may be precipitated, but what is more likely is that during the vaccination reaction the allergic symptoms may recede as they often do in the presence of intercurrent disturbances

Lapse of time from vaccination to protection successful vaccination per

formed on the day of exposure will almost always completely protect, performed up to a few days before onset of the disease it will at least make the attack milder. It is roughly true that the individual is protected completely twelve days after performance of vaccination, but since the vaccination may not "take" the first time it is tried, it may be wise if an individual presents himself within four days of the time of known exposure, to vaccinate twice, the second time two days after the first and 2 inches removed from it.

Duration of immunity it is estimated that protection in white persons lasts from seven to ten years, and in the Negro four years, but this is largely a gratuitous assumption using the magical numbers seven and ten. As a matter of fact, not many reliable data are in hand for the reason that all three types of "take" (see above) must be carefully observed and recorded if the statistics are to have value. Until very recently failure to obtain any sort of reaction was often interpreted as evidence of retained immunity, whereas we know that this only indicates unsuccessful vaccination. A recent authoritative study, that of Dearing and Rosenau (1934) on medical students at Harvard, indicated that the immunity conferred by a single vaccination lasts twenty years or more in most individuals, welcome news, but since 1 of the 22 students revaccinated less than five years after the first successful vaccination gave a primary "take" (evidence of complete loss of immunity), we are not helped much in determining the absolute minimum duration of protection. However, it may be that infection with smallpox is more difficult after successful vaccination with cowpox than is reinfection with cowpox on revaccination. At any rate, cases of smallpox are very rare within two or three years after a successful "take." Colonel Simmons (1941) says that in our new army revaccination will be required at intervals of three years, earlier if indicated by transfer to a theater of operations or in event of a threatened outbreak of the disease.

When and How Often to Vaccinate—In view of what has just been said above, it is apparent that we have no absolute guide. The following seems to be reasonable. Children should be vaccinated before six months of age, again on entering school, and again at puberty, all children and all adults should be revaccinated when there has been a known exposure, when an epidemic threatens, or upon visiting a region where foci of the old malignant form of smallpox are known to exist. If the newborn infant is mature at birth vaccination at this time is a safe procedure with negligible complications insignificant influence on growth and nutrition, and a very high percentage of "takes" almost always without fever (Dunnally *et al*, 1934-1940), but, as Doull (1934) has pointed out, the first day and week being the time of greatest mortality from other causes, some of these deaths may be erroneously attributed to vaccination.

Preventive Vaccination with New Type Vaccines.—It seems to me that studies of tissue culture vaccines for intradermal use, as devised by Rivers and by Goodpasture, are still sufficiently experimental that their inclusion in this book is not warranted as yet.

Immunization Schedule.—In 1937, Peterman, of Milwaukee, published an observation and immunization schedule for infants from birth to one year, early in 1942, Dr. Peterman kindly revised the schedule for me in accordance with his more recent experience and I include it here as a very practical guide for conduct of the first year of life.

At birth look for

- 1 Prematurity—weight under five pounds
- 2 Areas of atelectasis—treat with oxygen
- 3 Imperforate anus—have surgeon operate
- 4 Congenital heart disease
- 5 Hydrocephalus
- 6 Wryneck—correct early
- 7 Clubfeet—correct early
- 8 Dislocated hip with gluteal folds absent or shallow and trochanters not symmetrical—correct early
- 9 Jaundice

One month

- 1 Start cod liver oil and orange juice
- 2 Look for Erb's palsy and umbilical hernia—strap with waterproof adhesive after folding in umbilicus

Two months

- 1 Weight and measurement—monthly
- 2 Ability to hold up head
- 3 Check formula

Three months

- 1 Prevent thumb and finger sucking

Four months

- 1 Child's birth weight should be doubled
- 2 Add cereals to diet
- 3 Look for rickets and anemia will be found in half of the infants
- 4 Smallpox vaccination

Five months

- 1 Addition of more cereals to diet
- 2 Postural ability
- 3 Posterior fontanel closed

Six months

- 1 Postural ability (baby should sit up alone)
- 2 Add vegetables to diet—properly canned are preferable
- 3 Whooping cough immunization (Sauer vaccine)

Seven months

- 1 Add egg yolk to diet except in eczema

Eight months

- 1 Add scraped beef and baked potato to diet
- 2 Whole milk diet (no sugar)

Nine months

- 1 Diphtheria and tetanus toxoids combined—first injection
- 2 Add zwieback and mashed fruit and gelatin

Ten months

- 1 Should stand alone

Twelve months

- 1 Three meals a day
- 2 Final monthly examination
- 3 Baby starts to walk and talk
- 4 Examine urine
- 5 Diphtheria and tetanus toxoids combined—second injection (six weeks later Schick test and repeat every five years repeat tetanus toxoid every two years)
- 6 Complete physical report given to parents

SYPHILIS

Syphilis is a venereal and general constitutional disease, caused by *Treponema pallidum*. Whether or not it was unknown in the civilized world prior to the first return of Columbus from Haiti, in 1493, is a controversial point about which discussion is so warmly waxing in recent years that I now humbly hesitate to commit myself so fully as I did in earlier times. However, there is agreement on the following two points at least. That at the end of the fifteenth century syphilis was spreading widely throughout Europe (or the physicians of the Renaissance were suddenly awakening to its presence), and that recognition of the entity and realization of its importance have been steadily increasing since that period. The trend of the incidence of syphilis seems to be upward in many civilized countries today, though it is definitely declining in others, particularly in small countries with homogeneous, highly

literate, and easily accessible populations. Under the impact of the great attack upon the disease launched by Surgeon General Parran a few years ago a rapid decline in incidence is certain to occur in the United States, our record has been none too good and it is certainly to be deplored that such a campaign was not instituted long ago. Currently, Beerman (1940) states authoritatively that annually 500,000 patients with early syphilis seek authorized medical care, the number who neglect treatment is of course undetermined but it must also be huge. In such primitive races as have been investigated from this standpoint the incidence is usually found to be very high, for example, a 50 per cent infection rate based upon clinical observations only has been determined in certain nomadic tribes of eastern Siberia. Of very great interest are the observations of Hudson, who alleges that there is a Bedouin population in the valley of the middle Euphrates River in whom the disease, there known as *bejel*, exists as a completely nonvenereal contagious disease of children. There are those, however, who are doubtful of this nonvenereal characteristic, and Hasselmann, who undertook an investigation for the United States Public Health Service, flatly denies it. Some men look upon *bejel* and yaws as the same thing and others consider that *bejel* may be a disease intermediate between yaws and syphilis. The earlier belief that classical neurosyphilis does not occur among primitive peoples in whom primary syphilis is untreated is now entirely discredited, that its rarity in certain regions despite a high incidence of syphilitic infection *per se* may be due to the endemicity of malaria has been interestingly discussed, *pro* by Needles (1935), *con* by Franke (1933).

Syphilis is usually acquired by sexual intercourse with an infected person, but the incidence of innocent transmission is higher than is generally believed. In Clarke's (1939) analysis of 971 cases of syphilis diagnosed in the chancre stage in clinics of the New York Department of Health 5.7 per cent were found to be extragenital. The seriousness of early unsuspected syphilis of this type is evidenced in such reports as that of Rowntree and Hendon (1940) who found extragenital transmission of the disease among five persons in one family.

In the classical case of syphilis, venereally acquired, the course is generally the following: (a) The appearance of the primary sore (chancre) after an average incubation period of twelve to forty days. (b) The appearance of secondary symptoms at an average time of eight weeks after the appearance of the chancre: skin rashes of such varied sorts as to make description impossible here, mucous patches in the mouth, anal region, etc., plus the symptoms which often accompany general infections in greater or less degree, such as malaise, fever, anorexia, sore throat, headache and joint pains, and nervous manifestations, very rarely acute nephrosis. (c) A so-called 'latent period' during which the infection is apparently quiescent for a variable term of years. (d) The appearance of the 'tertiary' period of the disease, which is characterized by protean and serious symptoms which are due to gummatous, or more diffuse, pathologic disturbances which may occur in any portion of the body.

The above classification into primary, secondary, latent, and tertiary stages is largely arbitrary and is by no means clearly demarcated in all cases. The symptoms in congenital syphilis are in the main the same as those in the acquired variety except that the primary sore is lacking and that the type of damage peculiar to the tertiary period is usually caused early in the life

of the patient. The fetus is infected *in utero* by the mother, who must herself be first infected.

THERAPY

The reader will find the subject presented systematically under the headings listed below, but he is strongly urged to read the article in its entirety, slowly and thoughtfully, in order to obtain a broad picture of the modern therapy of syphilis before attempting to apply detailed treatment to a patient whose status places him in any one of the several categories

Early Syphilis	Cardiovascular Syphilis
Treatment resistant Syphilis	Syphilis in Pregnancy
Latent and Wassermann fast Syphilis	Congenital Syphilis
Early Neurosyphilis	Late (Tertiary) Syphilis
Late Neurosyphilis	Iodides in Syphilis

Prophylaxis of Syphilis

TREATMENT OF EARLY SYPHILIS

Very soon after Ehrlich's introduction of salvarsan in 1910 it became apparent that early syphilis could be sometimes cured, but it has required much detailed study and the passage of many years to determine precisely what the circumstances are which make such cures possible, and what conditions must be fulfilled if we are to realize the reasonable hope of curing every case through skilled chemotherapeutic attack from the very beginning. The rules of correct procedure are now taking very definite form, and I am therefore offering here a brief condensation of what has been revealed through the world wide investigation of the subject sponsored by the League of Nations Health Organization. This study has been carried through in the United States by the Cooperative Clinical Group, comprising the syphilis clinics of the Universities of Pennsylvania and Michigan, Western Reserve University, Johns Hopkins University, the Mayo Clinic and the United States Public Health Service. To make the findings of the Clinical Group available to the reader in a concise and usable form I have resorted to terse and rather dogmatic statement of conclusions without presenting the data upon which they are based, it is all available, however, to one who desires justification or elaboration of any single point—the references in the Bibliography to the work of the following men and their associates will lead into the literature. Moore, J. E., Cole, H. N., Stokes, J. H., O'Leary, P. A. The findings of the Clinical Group were published in the period 1934–1938. Since that time the authoritative Circular Letter No. 18 of the War Department, comprising the recommendations of the National Research Council on the treatment of military personnel has appeared (March 10, 1941), as have also a number of other valuable contributions of individuals and groups—all of which will be found incorporated and cited in the presentation below.

Importance of Early and Adequate Treatment—If the patient is not treated in the beginning of the infection, serious late syphilis may be expected in about 25 per cent of instances, benign late syphilis in 15 per cent, latent syphilis in 30 per cent, and spontaneous "cure" in 30 per cent. If the patient is treated early, continuously and inadequately, complete cure may be

expected in about 90 per cent of instances, with symptomatic cure but retention of a positive blood Wassermann in another 5 per cent. Therefore, in reply to the patient's question "what are my chances of becoming and remaining well with no further trouble from this disease?" the answer is "ninety five per cent if you are properly treated and if you cooperate fully and bear the drugs well."

When to Begin Treatment—From the diagnostic standpoint early syphilis is divisible into three stages (a) seronegative primary syphilis (chancre, but blood tests still negative), (b) seropositive primary syphilis (both chancre and positive blood tests), and (c) early secondary syphilis (the appearance of subjective and objective evidences of generalized constitutional involvement, of which mucocutaneous lesions may be a part, occurring either before or after disappearance of the chancre). It is now definitely known that the prospect of cure drops about 20 per cent if one waits to begin treatment until the blood tests become positive or the secondary manifestations appear but it should be remarked that this is "cure" in the purest sense of the word, *i. e.*, both symptomatic and serologic cure. Symptomatic cure alone can apparently be accomplished as well if treatment is begun in the early secondary stage as in the primary stage. Nevertheless, the obligation is to begin treatment in the seronegative primary stage if possible, in order to obtain academic as well as practical cure, but this does not imply the hasty institution of treatment before it is definitely known whether a suspicious genital lesion is actually the primary sore of syphilis. What is mandatory, if the patient is to be given his best chance, is to make early and repeated darkfield examinations of the local lesion, beginning treatment as soon as one such examination is positive, or in some instances, failing to obtain a darkfield view of the spirochetes, it may involve the performance of Wassermann tests on the fluids from the lesion in the endeavor to obtain a positive test which will warrant the beginning of a vigorous chemotherapeutic attack. I am aware that this will usually necessitate sending the patient to a laboratory, perhaps repeatedly, and that many men feel their diagnostic acumen enables them to recognize the chancre even though it has not assumed a "typical" form—but it is my duty to state the findings and conclusions of those whose large experience in this field entitles them to make the rules of correct procedure.

Personal Habits, Hygiene, and Ways of Living for the Patient—The perfectly cooperative patient will comply with the following requirements (a) Abstain not only from sexual intercourse but from all physical contact with other individuals or any articles whatsoever—pipes, towels, shaving paraphernalia, etc.—in use by others (b) Dishes to be scalded after use (c) Burn all dressings (d) Take good care of the teeth and when visiting the dentist tell him of the infection (e) Abstain from smoking and drinking (the harmfulness of tobacco in early syphilis is not proved but since smoking may predispose to dangerous leukoplakia at a later period, it is as well to attempt to break the habit in the beginning, alcohol probably harms principally by increasing the likelihood of occurrence of arsenical reactions, as well as inducing to a lowering of the bars of caution) (f) Live as calmly and quietly as possible consistently with obtaining requisite moderate exercise. The considerable importance of obtaining plenty of sleep and the relief from tedium afforded by an occasional vacation has been reemphasized by

Obermayer and Becker (1936) (g) Report pimples, hemorrhoids, coughs, colds, all other illnesses and indispositions to the physician

Superiority of Continuous to All Other Types of Treatment.—The following are the possible types of treatment (1) Continuous a course of one of the arsenicals, then a course of a heavy metal (bismuth or mercury), then arsenic, then metal, and so on through the requisite number of treatments—each course to follow the other without any intermissions whatsoever (2) Intermittent same as above but with a rest period between each of the drug courses (3) Combined the simultaneous administration of arsenic and heavy metal (4) Intensive much larger quantities of arsenic than are given in a short time in any of the above schemes, the idea being to overwhelm the infecting organisms with massive dosage administered during only a few days

Now what do the studies show? Precisely this that from all points of view the continuous method is superior to all the others, it gives the greatest percentage of cures, the highest percentage of Wassermann reversals in the first year, the lowest percentage of relapses Padgett (1941), of the Johns Hopkins group, has recently reported on the permanence of these cures in the first large scale, long term evaluation of treatment results in early syphilis to become available those of his 551 patients who were clinically and serologically negative five years after treatment ended were still negative after five or more years of further observation Moore's opinion is that these data justify the conclusion that in early syphilis five-year cure means permanent cure In this edition of the book I shall therefore continue to describe exclusively what has been called above the "continuous" method of treatment, but parenthetically two new experimental methods will be referred to briefly here

University of Chicago Combined Method—A short time ago, Becker began a trial of combined bismuth arsenical courses at the University of Chicago Clinics using fewer arsenical courses and closer together than is usual and giving bismuth continuously for the first forty to fifty weeks of treatment The results, as shown in the first report on 55 patients (Walsh and Becker, 1941), are certainly very good and will cause a continuation of these studies to be watched with much interest, but it may not be unwarranted to remind the reader that Beckb and Barnett (1939), in San Francisco, studied a not altogether dissimilar combined method in 81 patients, with 236 patients treated by the alternating method as control, and found that the incidence of relapse both clinical and serological was greater among the group receiving the combined treatment

Mount Sinai Five day Method—The newest departure in intensive methods—namely, the continuous intravenous drip of nearsphenamine or mapharsen during ten to twelve hours on four or five consecutive days—is an immensely interesting development in the therapy of syphilis which is being eagerly and hopefully watched by officials of the army and navy and public health services as well as by syphilologists, but the studies are still being pursued practically exclusively at the Mount Sinai Hospital in New York where they originated, and it is the unanimous opinion of all students of this new method that it is still in the experimental stage and by no means sufficiently developed as yet to warrant its trial by any other than a few highly specialized groups of investigators (There are full references to this work under the following names in the Bibliography Leifer, W., Bachr, G.,

this reference including all the papers presented and the discussion at the conference on the subject held on April 12, 1940, Chargin *et al*, Hyman *et al*.)

Drugs to Be Used—The arsenicals remain preeminent among antisyphilitic drugs for their ability to sterilize lesions quickly, prevent infectious relapse, reverse the Wassermann reaction and effect an ultimate cure. But no patient with early syphilis should be treated with arsenicals alone for the reason that by so doing we apparently make him especially liable to recurrences involving the nervous system, liver and other structures, or to the development of very destructive gummatous lesions only a few months after the primary stage. To prevent these things, one of the heavy metals must be used to supplement the arsenical therapy. Of the two metals bismuth and mercury, the former is now definitely known to be quite the superior—a superiority recognized not only on the basis of the private practitioner's impressions regarding its higher therapeutic efficacy and lower incidence of systemic and local reactions, but also thoroughly substantiated in large scale statistical studies. For example, in the findings of the Co-operative Clinical Group, it very clearly appears that if an arsenical and bismuth are used there is a 6 per cent lesser frequency of infectious relapse, and a 12 per cent greater frequency of serologic reversal, than if an arsenical and mercury are employed. But these metals alone, even bismuth are not suitable for exclusive use in the treatment of early syphilis. The rule is arsenical, bismuth (or mercury if for some reason bismuth cannot be given), arsenical bismuth, and so on and so on.

ARSENICALS SUITABLE FOR USE BY THE GENERAL PRACTITIONER IN THE TREATMENT OF EARLY SYPHILIS

The drugs deserving serious consideration for routine use in early syphilis are old arsphenamine, neoarsphenamine, silver arsphenamine, mapharsen and bismarsen. Sulfarsphenamine is much too toxic, and acetarsone (stovarsol) has not succeeded in making a place for itself. Indeed Robinson and Robinson (1939) have found that the latter not only is ineffective but is provocative of an unusually high incidence of reactions, they conclude that it is a 'dangerous' drug. Silver arsphenamine, though it has had several enthusiastic advocates, the latest being Cannon (1934-1939), has never caught on in this country and seems to me to be definitely not a drug for use by the general practitioner as its preparation and administration require a more complicated technic than with neoarsphenamine or mapharsen and the possibility of inducing argyria with it, though admittedly remote, lurks always in the background. Thioarsen trisodarsen, solu salvarsan and neocryl are still in the experimental stage. My feeling is that there are only three arsenicals suited to the needs of the general practitioner treating early syphilis, and I shall concern myself only with these three: neoarsphenamine, mapharsen, and bismarsen.

Neoarsphenamine—Practically all syphilologists are agreed that neoarsphenamine is actually inferior to old arsphenamine if the two drugs are given in the same dosage and for the same length of time. Nevertheless, for the general practitioner treating his cases in private practice, neoarsphenamine is undoubtedly the better drug to use. It is certainly easier to prepare and give than arsphenamine, it is freer from toxic reactions than the latter drug in the hands of the physician unequipped with either facilities or time for

proper solution, neutralization, etc.; and, if given in larger doses and longer courses than arsphenamine, it is probably nearly equivalent in therapeutic effectiveness.

Mapharsen—This is the name applied to arsenoxide which had been long rejected on the basis of alleged high toxicity until reinvestigation by Tatum and Cooper, in 1934, showed that at least in experimental trypanosomiasis and syphilis it actually had a low toxicity combined with a very high therapeutic efficiency. The subsequent independent clinical studies of many men have fully established the fact that in early syphilis in man the drug is nearly as effective as old arsphenamine and probably more effective than neoarsphenamine in causing disappearance of spirochetes, quick healing of visible lesions, and Wassermann reversal (see the following references in the Bibliography: Foerster, Wieder *et al*, 1935-1937, Grulizit and Dixon, 1936, Astrachan, 1937, Parsons, 1937-1940, Cole and Palmer, 1937, Marshall, 1937, Chargin *et al*, 1939, Rein and Wise, 1939). Of course we do not know as yet what the "staying power" of this drug is going to be as compared with neoarsphenamine, i. e., not enough time has elapsed to enable us to be sure that the 'cures' achieved with mapharsen will be as permanent as those with neoarsphenamine, but I do not know any disinterested student of the subject who believes he has any reason to feel that they will not be. The great advantages of mapharsen over neoarsphenamine, which are causing it to become the preferred drug in many quarters, are (a) The technique of its preparation for administration is just as simple as that of neoarsphenamine but unlike the latter drug it becomes less toxic while standing in solution and it may, indeed should, be injected rapidly. (b) The incidence of serious toxic reactions of all sorts is distinctly less, as indicated in several reports and clearly shown in Epstein's (1941) compiled data from 92,000 injections. (c) The most annoying and most frequently occurring reaction with neoarsphenamine—the nitritoid reaction—practically does not occur with mapharsen at all. Stokes and Beerman (1941) point out that one of the strongest tributes to the low toxicity of mapharsen is its fine record when substituted for neoarsphenamine in the experimental studies with the five-day intensive treatment method, previously referred to. (d) Mapharsen may often be satisfactorily substituted for other arsenicals which have proved reaction producing.

Bismarsen—This, a combined bismuth arsphenamine salt which is given intramuscularly and is easy to prepare for injection, has had a longer trial than mapharsen, but it still has not made much of a place for itself by comparison. Stokes and Beerman (1941) feel the substance of all the published evaluation of the drug is that it is at its best in children and in cardiovascular syphilis. Observers are agreed that disappearance of spirochetes and healing of the primary sore, and of the condylomas, mucous, macular, papular, etc., syphilids of the secondary stage, proceed considerably slower under bismarsen than under arsphenamine or neoarsphenamine. O'Leary, who was once quite favorably inclined toward the drug, has rejected it on the basis of a higher proportion of relapses, particularly in the nervous system, than under other types of treatment. Kolmer believes that it is not the drug of choice unless intravenous medication is impossible. In the matter of systemic reactions bismarsen is probably equivalent to neoarsphenamine but with apparently a greater tendency to cause hematopoietic injury. Local reactions of pain and

stiffness, most marked on the second and third days, usually occur with the early injections and are much reduced by massage, but in a relatively large proportion of cases they are severe enough to cause the drug to be abandoned.

I retain bismarsen in the book solely because in the rare case in which it is not feasible for the general practitioner to alternate intramuscular courses of bismuth with intravenous courses of mapharsen or neoarsphenamine, this is a third drug to which he may turn.

ADMINISTRATION OF NEOARSPHENAMINE, MAPHARSEN AND BISMARSEN IN EARLY SYPHILIS

Preparation and After-care of Patient—Before starting the arsenical course careful physical and urine analyses should be made, and the patient's full history elicited in order to determine whether one or more of the following conditions obtain. Evidence or history of skin hypersensitivity (chronic urticaria, eczema, seborrheic dermatitis, frequent "rashes") will indicate the necessity of starting with much lower than usual doses. There is evidence that untreated syphilis adversely affects the course of pulmonary tuberculosis and that treatment of the syphilis checks the progress of the tuberculous process (Smith, 1938, Goldblatt, 1939). The impression has been that a precautionary lowering of arsenical dosage is advisable and that if the tuberculous state is far advanced and cachectic, bismuth had best not least begin the treatment, yet Smith, who began treatment on this principle in the earlier cases in his series of 69 double infections, increased his dosage up to just about adequate for uncomplicated syphilis toward the end. If the patient is pregnant, is jaundiced, or has a liver or cardiovascular involvement, see the sections dealing with these conditions later in the chapter. In hyperthyroidism, Stokes (1934) finds such explosive reactivity to the arsphenamines that he prefers to control the hyperthyroidism before beginning antisyphilitic therapy. History of marked easy bruising should make one very cautious in the use of arsphenamines, and evidences on mucous membranes or skin (or reliable history) of purpura is probably sufficient to contraindicate the use of these drugs, tendency to lightly induced and prolonged hemorrhage should also be taken as warning of delicate balance in the blood-forming mechanisms. Mild nephritis counsels caution and initial dosage reduction and so does mild diabetes, untreated diabetes, especially if acidotic, had better be controlled before the arsenical treatments begin, unless the patient is in the advantageous seronegative primary stage of syphilis, which will warrant beginning both treatments simultaneously. Primary anemia necessitates dosage reduction in the beginning, but secondary anemia is usually quickly benefited by the arsenicals, antirheitics and hypertensives are often helped. Optic or acoustic nerve involvement necessitates preparatory use of a heavy metal for three to six weeks (Stokes, 1934). Constipation not infrequently disappears during treatment, since the arsphenamines tend to induce moderate diarrhea, it is customary in the practice of many men to have a saline cathartic taken on the morning after each injection. If the patient cannot lie down for several hours immediately following the injection he should at least avoid physical exertion as much as possible.

Diet During Treatment—The meal preceding the injection and the next one following it should consist of nothing more than toast and coffee or tea, and nothing at all should be placed in the stomach for at least two hours be-

fore the injection. It does not seem to me that at present one can say with very great assurance just what the diet should be during the arsenical courses. Until recently it had been the almost universal custom to place the patient on a high carbohydrate and low fat and protein diet, usually accomplished by forcing the taking of much bread, potatoes, and cereals through a great restriction in the allowance of meat, fish, eggs, milk, and butter. The belief had been that the liver was thus to some extent protected against the hepatotoxic action of the arsenicals. Latterly, however, attention has been called to the possible advisability of reversing this regimen in order to give much protein and fat and keep the carbohydrate low (allow meat, milk, eggs and butter in abundance but greatly restrict the consumption of bread, potatoes and cereals and prohibit entirely the taking of sugar, candy, and sweet or starchy desserts, fish and sea food are probably always best prohibited since many individuals are hypersensitive to these foods). The experimental study of Craven (1931), which first suggested the trial of this new type of diet, has been confirmed by Messinger and Hawkins (1940) in that they found protein more protective than carbohydrate, but they found the inclusion of fat distinctly deleterious. With Beerman (1934), I feel that the validity of applying findings in carnivorous dogs to dietary problems in omnivorous man is certainly questionable. However, Stokes (1934) states that he has seen the value of this new dietary regimen confirmed not in hepatic protection (this point he it remarked, is still open) but in the prevention of cutaneous irritability. Many individuals who experience some degree of diarrhea while on arsenical treatment are much helped by greatly reducing the consumption of fruits and coarse vegetables.

I do not know of any evidence that stuffing with any of the vitamins is of benefit.

Preparation of Neoarsphenamine Solution—The powder should be lemon to canary yellow, if the color approaches red and the drug is lumpy or solidified it should not be used. Pour about 5 cc of sterile distilled water (the more recently distilled the better probably) into a sterilized beaker. Dip the ampule into alcohol to detect a possible crack, and then when it dries after removal file it open and pour the contents onto the surface of the water, allow solution to take place without shaking the beaker because agitation will increase the oxidation of the drug and thus greatly increase its toxicity. Solution made directly in the ampule is very likely to be more toxic than that made as above described. It should not require more than five minutes to dissolve the drug completely, and the solution should be rejected if much more than ten minutes is necessary to accomplish this. The use of a small horse needle is nowadays generally considered sufficient protection against the injection of small particles of glass which might conceivably have got into the solution, but a few men still use the syringe filtering adapter devised by Schamberg a number of years ago. Inject as soon as possible in no case using a solution which has been fully ready for more than twenty minutes, unless it has been all the while in the syringe without air bubbles. *Inject very slowly!* The drug should be stored in the ampules in a refrigerator and in making the solution water at room temperature is used, the toxicity increases rapidly above 71° F (21.7° C). Do not use ampules more than six months old.

Preparation of Mapharsen Solution—Mapharsen is a white powder, it should not be used if it is gray, brown, or black. A recent note from the Navy

medical department (War Medicine, 1, 429, May, 1941) indicates the advisability of storing the ampules in the refrigerator. The precautions against oxidation of the drug, so important with nearsphenamine (see above) are not necessary here, indeed, maparsen becomes less toxic on exposure to air and therefore agitation of the solution during preparation is desirable. The solution is made using 1 cc. of sterile, distilled water for each 4 mg. of the drug but not to exceed a total of 10 cc.

Intravenous Administration of Nearsphenamine and Maparsen—The essential steps are the following: (a) Have patient reclining on back with arm hared to well above elbow and lying at ease along the side (extended at right angles is possibly preferable but seldom to be achieved in the average office). (b) Apply tourniquet above elbow and wipe the injection site with 70 per cent alcohol on cotton. (c) Eject all air from syringe and needle, and introduce needle into vein. (d) Draw back on plunger and be sure that a full sized stream of blood enters syringe quickly and freely, some men use a 20-cc. syringe so that they can mix a number of cubic centimeters of blood with the solution before injecting. (e) Remove tourniquet and begin the injection. (f) Inject nearsphenamine very slowly the United States Public Health Service standard rate is 0.1 Gm. per thirty seconds, but ample experience of many men has shown that much slower injection than this is advantageous—the slower the better undoubtedly! The use of a small bore needle helps prevent rapid administration, Stokes advises that a 26 gauge, 1 inch needle be employed. (g) Maparsen can be injected intravenously as rapidly as one wishes, indeed, from the standpoint of preventing pain from venous spasm (see under Reactions), the faster the better. (h) At the conclusion of the injection bring the needle out quickly and apply at once a small bit of sterile cotton to the site of entry, the patient may hold the cotton in place with moderate pressure until bleeding stops and then the site may be wiped clean with a little alcohol on cotton.

The mastery of intravenous technic can only be gained under competent instruction and I earnestly counsel the reader to spend a little time in the nearest syphilis clinic before beginning the administration of nearsphenamine or maparsen in his private practice.

Preparation of Bismarsen Solution—The drug is dissolved in the ampule by injecting into it, at the rate of 1 cc. per 0.1 Gm., the solvent supplied by the manufacturer (containing 0.25 per cent butyn for local anesthesia).

Intramuscular Administration of Bismarsen—Replace the needle used in preparing the solution with a clean dry one and insert it to point down and slightly in from a point in the inner part of the upper outer quadrant of the buttock. After carefully aspirating (important!) to be sure that the point is not in a blood vessel, inject slowly and finish by detaching syringe, drawing up 1 to 2 cc. of air, and injecting this to prevent drawing some of the drug out toward the surface as the needle is withdrawn, which might later cause a painful button of induration.

Massaging deeply for several minutes, protecting the injection site by a pledget of alcohol soaked cotton in the hand, perhaps aids in the distribution of the drug and lessens the incidence of severely painful reactions.

Dosage of the Arsenicals—See the chart, on opposite page.

CHARTED SCHEME FOR TREATMENT OF EARLY SYPHILIS BY THE GENERAL PRACTITIONER

As = Arsenic

(Condensed from the text)

Bi = Bismuth

Weeks	1st day	As	Continued from below left	Notes
1	5th day	As	41	<p><i>Notes of the Scheme</i></p> <p>(1) Treatment to begin as soon as diagnosis can be made with certainty</p> <p>(2) Superiority of continuous treatment to any other type</p> <p>(3) Superiority of arsenicals for beginning the attack but necessity of using bismuth as supplementary drug, mercury definitely inferior</p> <p>(4) Neosaphenamine, mapharsen and bismarsen, the only arsenicals suited to the private practitioner's needs</p> <p>(5) Length of treatment to be about 12 months (48 weeks) in seropositive primary and 18 months (80 weeks) in seropositive primary or early secondary cases.</p> <p>(6) Time to be about equally divided between exclusive use of arsenic and bismuth, with overlapping of drugs at beginning and end of course</p> <p>(7) Advantages of ending either the 12 or 18 months' treatment with bismuth rather than arsenic.</p> <p>(8) Serological findings should not affect the treatment in any way routine testing during either the 12 or 18-month period may be omitted but blood and spinal fluid must be negative at the end</p>
2	10th day	As	42	
	15th day	As	43	
3		As	44	
4		As	45	
5		As	46	
6		As	47	
7		As	48	
8		As	49	
9		As	50	
10		As	51	
11		As	52	<p><i>Neosaphenamine</i></p> <p>First dose to be 0.3 Gm. All doses thereafter to be 0.5 to 0.7 Gm. (rarely as high as 0.9 Gm.) for men and 0.45 to 0.6 Gm. for women, depending on size and condition in both sexes</p>
12		As	53	
13		As	54	
14		As	55	
15		As	56	
16		As	57	
17		As	58	
18		As	59	
19		As	60	
20		As	61	
21		As	62	<p><i>Mapharsen</i></p> <p>First dose to be 40 mg. for men, probably 30 mg. for small women. All doses thereafter to be 40 to 60 mg. depending upon size and condition.</p>
22		As	63	
23		As	64	
24		As	65	
25		As	66	
26		As	67	
27		As	68	
28		As	69	
29		As	70	
30		As	71	
31		As	72	<p><i>Bismuth</i></p> <p>Other things being equal (see the text) the following N.Y.R. preparations fit best into the present scheme since they may be routinely administered in courses as long as ten weeks.</p> <p>Ampules bi-pot. 2 cc. (biposoluble) 1 ampule weekly</p> <p>Bismocymol ampules 2 cc. (biposoluble) 1 ampule weekly</p> <p>Bismocymol ampules 1 cc. (biposoluble) 1 ampule twice weekly</p> <p>Ampules bismuth sod. tart. 2 cc. (water sol.) 1 ampule thrice weekly (first injection, $\frac{1}{2}$ ampule)</p> <p>Ampules bismuth subarsenyl, 1 cc. (oil suspens.) 1 ampule weekly</p> <p>Emulsion mercur. (oil suspens.) 1 cc. weekly (first injection, $\frac{1}{2}$ cc.)</p> <p>Ampules closo-bis. Roche, 2 cc. (oil suspens.) 1 ampule weekly</p> <p>Ampules pot. bis. tart. with butyn, 2 cc. (oil suspens.) $\frac{1}{2}$ to 1 ampule weekly</p> <p>Tartro-quinosol ampules 2 cc. (oil suspens.) $\frac{1}{2}$ to 1 ampule weekly</p> <p>Sobumol solution, 2 cc. 1 ampule twice weekly</p> <p>Use of the following preparations, not believed as suitable as those above for prolonged administration will necessitate some alteration in the scheme which had best consist in curtailing its length at the bismuth course rather than in reducing very much the overlapping—especially in the first end of the first arsenic course</p> <p>Bismocyl ampules, 1 cc. (water sol.) 1 ampule thrice weekly (20 doses)</p> <p>Ampules pot. bis. tart. (aqueous), 2 cc. (water sol.) 1 ampule thrice weekly (15 doses)</p> <p>Quinosol ampules, 2 cc. (biposoluble) 1 to 2 cc. twice weekly (14 doses)</p> <p>Ampules duo-bismol 0.2 Gm. (dissolve in 1 cc. sterile water just before use) twice weekly (15 doses)</p> <p>Ampules sobumol with saligenon, 2 cc. (biposoluble) 1 ampule twice weekly (12 doses).</p>
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ARSENICAL REACTIONS IN EARLY SYPHILIS

It should be noted that all the reactions discussed below, with the exceptions to be indicated, occur much less frequently with mapharsen than with neoarsphenamine or hismarsen and that with mapharsen the nitritoid reaction apparently does not occur at all (Levin and Keddie [1942] found no report of a case of true nitritoid reaction in their thorough study of the literature)

Nitritoid Reaction—This type of reaction (not seen with mapharsen) usually begins shortly after the neoarsphenamine injection has been started or the hismarsen has been placed in the buttock. There may be sudden intense pain in the back though this is very rare, always, however, there is a quick general or blotchy flushing of the face and neck and injection of the eyes, dyspnea, cough, nausea and anxiety, sometimes, though unusually, the patient vomits at this point, usually the pulse becomes momentarily bounding and then very weak and edema of the face and neck may supervene. Sometimes there is loss of consciousness with suspended respiration for a few seconds. The symptoms usually persist for half an hour in some degree, sometimes longer. Though frightening to witness, the nitritoid reaction is fatal only in extremely rare instances. The often fatal colloidoclastic shock with somewhat similar symptoms, which occurs as the result of faulty preparation or administration of old arsphenamine, need not worry the practitioner using neoarsphenamine or hismarsen but he should be prepared for the patient's thorough fright through one such nitritoid experience, and he must heed the instructions for preparation and slow administration if he is to avoid frequent occurrence of this type of reaction with neoarsphenamine.

About the only effective treatment for the nitritoid reaction is the immediate subcutaneous or intramuscular injection of 0.5 to 1 cc. of epinephrine hydrochloride (adrenalin) 1:1000 solution—the arsenical injection having been stopped, of course. It is sometimes possible to prevent the recurrence of this reaction by the subcutaneous injection of 1/75 to 1/50 grain (0.0008–0.0012 Gm.) of atropine sulfate fifteen minutes before the injection, or epinephrine may be given before the injection instead of after the symptoms have appeared. Ephedrine sulfate is sometimes used, several doses of $\frac{1}{2}$ grain (0.025 Gm.) by mouth on the day before and the day of the injection.

Lacrimation-Salivation Reaction—A reaction apparently peculiar to mapharsen consists in mild lacrimation with mild to profuse salivation, beginning fifteen minutes to three hours after injection and lasting several hours. The reaction seems to be annoying rather than truly distressing.

Gastro-intestinal Reactions—Many individuals are much disturbed by an "ether like" odor and disgusting taste while neoarsphenamine is being injected. This may be counteracted by causing the patient to smell hay, rum or a perfume during the operation (the cheaper perfumes are preferable because of their greater pungency), place on a pledget of cotton and not on the clothing in order to avoid later embarrassment to the patient. Some individuals derive equal comfort from the rapid mastication in quick succession of several pieces of fresh wintergreen chewing gum.

When stomatitis occurs during arsenical administration it is almost always of a dry red type, usually accompanied by chapping of the lips, and hardly to be confused with the stomatitis of bismuth or mercury. Its chief significance is that it may be a warning of idiosyncrasy for the drug which will eventuate in serious dermatitis or hematopoietic damage if administration is persisted in.

Occasionally a patient will have more than the three or four stools which often follow in the few hours after the injection of an arsenical, and it may be necessary to give a dose of castor oil or very rarely an opiate. Milk toast, made from hoiled milk, for several meals succeeding the injection usually suffices to check the trouble in patients who have this diarrheal tendency. The drug effect is not lost by reason of these loose stools. Severe gastro-intestinal complications, such as the fatal neoarsphenamine gastric necrosis reported by Christianson (1935), are extremely rare. The rubber tubing type of reaction, which has a gastro-intestinal phase and is of serious moment in clinics where old arsphenamine is administered, does not concern us here.

Many physicians have found their patients experiencing fewer gastro-intestinal reactions under mapharsen than under neoarsphenamine. Levin and Keddie (1942) say that about 90 per cent of patients who have severe gastro-intestinal reactions to the arsphenamines can tolerate mapharsen in therapeutic doses.

Skin Reactions—Urticaria or a scarlatiniform erythema often occurs during the nitritoid reaction and subsides with it. Or such an eruption, accompanied by fever but not associated with nitritoid phenomena, may be experienced following one of the early injections and ordinarily not recurring. These fleeting skin involvements do not usually require any treatment. Generalized itching unaccompanied by dermatitis and following upon the injection of an arsenical is generally looked upon as a warning signal that further arsenical treatment if given at all should be under the supervision of a specialist. Interest is what is known as "ninth-day fever" in Europe was revived in this country by Keim (1935), scarlatiniform or morbilliform eruption occurring on the eighth to twelfth day after one of the early injections together with chill and fever, pharyngitis, vomiting, pains throughout the body, superficial adenopathy, and perhaps photophobia as in measles. There may also be subsequent desquamation as in scarlet fever. The reaction is nearly always over in five to seven days, but Muir (1937) reported a case which was followed by severe neuritis and later by severe vesicobullous dermatitis and death from toxic degeneration of internal organs. In Robinson's (1938) case, which developed after the third injection of neoarsphenamine, treatment was stopped for two weeks, upon its resumption after full recovery of the patient, hepatitis and jaundice developed very promptly. He, as well as Epstein and Levin (1939) and Canizars and Thomas (1939), reporting 6 and 11 cases respectively, feel that arsenical treatment should be resumed with caution after one of these reactions, the first dose being reduced in quantity. There is also occasionally seen a 'fixed' type of eruption which does not contraindicate continuance of treatment: one or more plaques which redden and swell, perhaps even become bullous, following each injection, residual pigmentation fades very slowly. Mendelsohn (1940) has reported an interesting case in which sharp pain in the jaw recurred with each fixed eruption. If to this brief sketch is added the occasional herpes zoster or erythema multiforme type of eruption and the very uncommon eczematous weeping eruption, practically all the skin involvements will have been covered except the most important one—exfoliative dermatitis which accounts for many of the deaths occurring under treatment of syphilis with the arsenicals. This reaction may occur at any time in any individual but the 4 fatal cases observed by the Cooperative Clinical Group were in young people with early syphilis and the reaction appeared after the third or

fourth injection. Briefly, the entity has the following characteristics: (a) general flush, with dry or moist dermatitis of flexor surfaces and lower parts of the body, accompanied by very severe itching, (b) usually some degree of edema and a septic temperature, (c) practically always a sensation of great chilliness, (d) the full picture may be established in a few hours after an injection and death may occur very early with intercurrent respiratory or myocardial symptoms, (e) the patient may linger many weeks or months with the skin becoming very scaly and secondarily infected, the body wasting away (Cannon *et al* [1942] redirect attention to the interesting poikiloderma-like changes which occur ultimately in extremely rare instances), liver, kidneys, intestinal tract and bone marrow becoming involved, and death finally occurring through these complications or an intercurrent pneumonia. Any general practitioner having the misfortune to have a patient develop exfoliative dermatitis will certainly make every effort to get him into a hospital and to have specialist consultation. The chief elements of treatment seem to be the following:

(A) The use of the alkaline colloid bath, as described under Eczema Dermatitis. Be sure to get the bland ointment on quickly after removal from the tub else misery will only be increased by these baths.

(B) Under Eczema-Dermatitis are described measures useful in the early stages of a dermatitis. Stokes warns against the use of any directly antipruritic agents, such as phenol, which he feels always aggravate these cases of arsenical dermatitis. Hollander (1936) has employed 5 per cent aqueous solution of tannic acid, either sprayed all over the body or applied as a wet dressing with satisfaction.

(C) Use warm saturated boric acid solution for syringing ears and bathing eyes, argyrol (10 per cent) if the conjunctivitis becomes purulent.

(D) Do everything possible to dissuade the patient from scratching and to prevent secondary infection: clean linens and bedclothes and thoroughly cleaned tub.

(E) Keep up nutrition as well as possible, both for constitutional protection and as safeguard against development of bed sores.

(F) Sodium thiosulfate. Denme and McBride introduced to the American profession in 1924, the French practice of using this drug. It is given intravenously in 20 cc. of sterile distilled water every day for four days, and then every other day for as long as is necessary. An ascending dosage is used: 0.3, 0.45, 0.6, 0.75, 0.9, 1.2 and 1.8 Gm. In fulminating cases the dose may be started higher and be given several times in the first twenty-four hours. Chemically pure and not the ordinary sodium thiosulfate should be used, it is said (Throne and Myers, 1935) that the prepared solutions on the market are less reliable than those extemporaneously made. I believe that most syphilologists are no longer particularly enthusiastic about the efficacy of sodium thiosulfate, Stokes says that in his opinion all it can do will be accomplished by the first 3 or 4 injections and that continuation beyond the sixth to eighth day may be injurious in severe cases. The chief claim in favor of this drug has been based upon the supposition that it mobilized excessive arsenic stored in the body, but no factual evidence in substantiation of this emerged in the recent study of Ceder *et al* (1941) of the United States Public Health Service. These workers used 10 syphilitics who had just completed a neoarsphenamine course, 6 received sodium thiosulfate, the other 4 were used

as controls. The drug did not significantly affect either the urinary, fecal, or total arsenic excretion.

(G) To discontinue arsenical treatment should certainly be the rule for the general practitioner, whether it may be cautiously resumed in a given case is a question to be answered only by the experienced specialist in close touch with the patient. Schoch *et al.* (1940) believe, as a result of considerable study, that mapharsen can usually be successfully used in patients after recovery from dermatitis produced by neoarsphenamine but only if the dermatitis has been of lesser severity than severe exfoliative dermatitis necessitating hospitalization, they recommend that mapharsen dosage be begun at 1 mg. and be very gradually built up, *i. e.*, requiring 10 to 14 injections to reach a 40 to 60 mg. dose.

Unfortunately, a patient who has survived an arsenic induced exfoliative dermatitis may be plunged into a second attack by the use of any of the other antisyphilitic drugs.

(H) Cormia (1941) gave massive vitamin C (ascorbic acid) dosage, both intravenously and by mouth to a small number of patients who had experienced arsphenamine dermatitis and felt that they were subsequently able to tolerate more of the arsenical, but he also felt that at times such vitamin therapy may diminish neoarsphenamine effectiveness. Much water must flow under the bridge before certainty is reached in this subject, it seems.

Hepatic Reaction—Around the pleasant little point of jaundice and hepatic injury in syphilis there has been spinning a considerable difference of opinion almost continuously since the arsphenamines came into general use. It seems to me that the studies of Wile and Sams (1934), and Sager (1936), most notable among numerous others, have established the following points with reasonable assurance of their truth.

(A) In a certain exceedingly small proportion of individuals with untreated secondary syphilis jaundice appears merely as one of the evidences of the generalization of the early toxemia.

(B) In individuals undergoing treatment with one of the arsenicals, this symptom occurs with much greater frequency.

(C) In most instances the fully developed clinical picture so closely resembles the familiar one of catarrhal jaundice as to make differentiation of the two conditions impossible save on the basis of history alone.

(D) The onset of symptoms may take place at any time during, or as long as ten months after, completion of the arsenical course.

(E) In a small proportion of the cases full acute yellow atrophy of the liver develops suddenly developing chills and fever, abdominal pain and liver tenderness, vomiting, delirium, prostration, coma, death.

(F) In neither syphilitic cirrhosis, diffuse hepatitis nor hepatic gumma—the typical forms of anatomic tertiary syphilis of the liver—does this picture develop.

(G) The syndrome is not merely a type of Herxheimer reaction, as might be suspected in instances when it appears following one of the early injections, nor is it the mere recurrence of active syphilis affecting the liver only (hepato-recurrence), as has been contended when it occurs following a lapse in treatment.

(H) It does not merely represent the coincidental occurrence of catarrhal jaundice in a patient with syphilis.

(I) It is caused fundamentally by the toxic action of the drug on the liver,

but a coincidental epidemic of catarrhal jaundice may certainly predispose an individual to the development of this type of direct arsenical injury.

Nowadays it is sometimes considered advisable to continue treatment in the presence of jaundice which has appeared after the administration of an arsenical, the picture clearing slowly while treatment is being continued, but this is certainly dangerous procedure for the general practitioner, and I think that he is still well advised to discontinue the use of arsenic in any patient becoming jaundiced unless he has the advantage of studying his case in consultation with a skilled syphilologist. In combating the liver injury itself, carbohydrates are usually pushed. Soffer (1939) likes to get in 400 to 600 Gm daily and employs the continuous intravenous drip (venoclysis) of 5 per cent dextrose if the high carbohydrate diet is not well accepted. Appel and Jankelsohn (1935) favored the frequent intravenous injection of 10 cc of 5 per cent sodium dehydrocholate (decholin), but there has certainly not been general acceptance of this therapy. Soffer agrees with Ottenberg (1935) that to give cholagogues in postarsphenamine hepatitis has no more rationale than the use of diuretics in acute nephritis.

If the patient presents with jaundice, *i.e.*, in the presence of early syphilitic hepatitis with jaundice in an untreated patient, Stokes advises preparatory treatment with bismuth for three to six weeks before instituting arsenical therapy, certainly most men agree with and follow the practice but the number of such cases is not large and therefore we have no real assurance that arsenicals begun in small dosage would be more harmful than bismuth—there have been a few recent reports of isolated cases treated with arsenicals from the beginning with no apparent harm (Vaughn, 1937, Creswell *et al.*, 1939, Rattner and Reiser, 1941).

Hematopoietic Reactions—Fortunately, in view of the extremely high fatality rate, arsenic injuries to the blood forming apparatus are rare. McCarthy and Wilson's (1932) review established the vast majority of cases as being classifiable as follows: (a) thrombocytopenic, with typical purpuric or external hemorrhagic features, (b) granulocytopenic, presenting the picture of a fulminating agranulocytosis, and (c) aplastic, with the characteristics manifested when all the cellular elements of the blood have been affected. Symptoms may appear after any injection in any one of the courses. Bronfin and Singermaa (1932) recommend frequent blood examinations in every patient under treatment with any of the arsenicals even in the absence of untoward manifestations, and the immediate discontinuance of the drug as soon as such symptoms as malaise, pallor, itching of the skin or purpuric signs are noted. Such forehandedness would probably not be entirely practicable in most practices, but there can be no doubt of the bounden duty to be alert to the possibility of hematopoietic injury, and never again to give any of the arsenicals to a patient who has manifested the least signs of such injury.

The experience of Epstein and Falcoer (1940) indicates that mapharsen usually will not cause a reproduction of the purpuric reaction in patients exhibiting this type of dyscrasia; they did not find that vitamin C (ascorbic acid) altered the tendency in any way. There are also indications from scattered case reports that mapharsen can often be safely substituted for neoarsphenamine in individuals who have experienced an attack of agranulocytosis from the latter.

Nervous System Reactions—Hemorrhagic encephalitis, which may occur

without any warning signs after any but especially the earlier injections, is very rare and very often fatal. The symptoms usually develop two or three days after the treatment: headache, giddiness, apprehension, delirium, vomiting, urinary and fecal incontinence, convulsions, coma, and death in forty-eight hours. Netherton (1934) has reported two recoveries, perhaps the cases were not of the most severe sort—still, they recovered, and it is worth noting what he did: (a) epinephrine hydrochloride (adrenalin), 2 cc of 1:1000 subcutaneously every two hours until improvement is noted; (b) sodium thiosulfate injections (see under skin reactions); (c) 500 cc of 25 per cent dextrose solution intravenously twice daily; (d) magnesium sulfate 15 grains (1 Gm), and morphine sulfate, $\frac{1}{2}$ grain (0.015 Gm), as anticonvulsant and sedative; (e) lumbar puncture, provided there is no choking of the optic disks, for both diagnostic and therapeutic purposes.

Myelitis and encephalomyelitis are even more rare and more often fatal than encephalitis. A mild degree of nerve irritation, usually going no further than the development of numbness and formication in the extremities, is not rare during administration of arsenicals, neoarsphenamine being a frequent offender in this respect. Severe cases of true multiple neuritis are extremely rare; sodium thiosulfate is often given in these cases and arsenicals are omitted from subsequent therapy. In a recent case of arsenical peripheral neuritis following the ingestion of arsenic trioxide in the form of rat poison, Vilter *et al* (1940) had good results with 50 mg daily of thiamine hydrochloride intravenously in physiologic saline solution; improvement was more striking when 50 mg of alpha tocopherol were also given intramuscularly.

Herxheimer Reaction ("Therapeutic Shock")—This consists in a lighting up of all the syphilitic lesions, appearing in early syphilis from a few hours to a day after the first injection of an arsenical—perhaps more abruptly with mapharsen than with neoarsphenamine or hismarsen. The reaction disappears slowly during several succeeding days and very rarely recurs following subsequent doses. "Herxheimer" is usually of little moment in early syphilis because of the nature and location of the lesions, but the liability of its occurrence constitutes one of the reasons for making the first dose of an arsenical smaller than the subsequent doses; in late syphilis with its numerous visceral lesions, very grave symptoms may accompany such a reaction—which fact often dictates therapeutic approach to late syphilis through preliminary use of heavy metals.

Prevention of Subsequent Reactions—The findings of the Cooperative Clinical Group—which, be it noted, were reported before much experience had accumulated with mapharsen—may be summarized as follows:

(A) If treatment is continued and no precautionary steps are taken at all, 61 per cent of individuals will react again.

(B) If it is imperatively necessary to continue arsenical treatment, changing the drug is the most successful method of avoiding further trouble; only 35 per cent of the patients will again react.

(C) Next best to changing the drug is merely to reduce the subsequent doses; 45 per cent will react.

(D) The absolutely best assurance of avoiding a further reaction at any time is to postpone the next dose, if this is feasible, at least a month, preferably three to six months, after such postponement neither changing the drug nor reducing the dose seems to give any added advantage.

Detoxifying Agents—Doak (1911), of Johns Hopkins, has reviewed the subject of all the agents supposed to have a detoxifying effect when administered with the arsenicals, his conclusion is that none of them have been shown to have established worth

Capillary Resistance Test—The studies of Horne and Scarborough (1941) indicate that intolerance to arsenicals may be associated with decreased capillary resistance. Attempt should be made to confirm these observations upon a large scale and soon, since the routine performance of a Rumpel-Leed test would be well worth the few moments required if it should prove helpful in segregating at least those most likely to be adversely affected by arsenicals

Accidental Paravenous Infiltration of Neoarsphenamine or Mapharsen—Treat by withdrawal of needle and immediate injection from another syringe, of 20 to 30 cc of physiologic saline solution containing 0.5 per cent procaine hydrochloride (novocain), placing the solution around and in the infiltrated area. Then complete the arsenical injection at another site. Cold compresses are usually helpful in the beginning, later, hot compresses of saturated solution of magnesium sulfate may be used

Venous Spasm—When injecting old arsphenamine, with which we are not concerning ourselves in this book, pain along the vein is sometimes observed during or immediately after injection. Such pain has recently been reported to occur not infrequently if mapharsen is injected slowly. An important point noted by Schoch (1936) is that cold, not hot applications, laid from elbow to shoulder along the anterior surface of the arm, will quickly stop this pain

BISMUTH PREPARATIONS SUITABLE FOR USE IN EARLY SYPHILIS

Bismuth is very likely to cause severe reactions and even death when given intravenously, and can be injected safely and with good effect only intramuscularly. Unfortunately there are three types of salts offered for intramuscular use, and we must attempt to understand the differences in their properties and activities. Latterly, a bismuth preparation suitable for administration by mouth is receiving some clinical attention and must also be discussed in what follows

Water-soluble Salts for Injection—These preparations are more rapidly and more regularly absorbed than the oily suspensions, which is both an advantage and a disadvantage. Advantageous, in that it enables quick results to be attained, disadvantageous, in that most of them must be administered thrice in the week, and are thus difficult to use even in office practice except in unusual instances. Furthermore, these aqueous solutions are very apt to cause troublesome stomatitis if they are pushed too rapidly. An advantage, on the other hand, is that there is no danger of embolism or infarction following these injections—which, however, are much more painful than are those of the oily suspensions. For a list of the chief preparations, dosage, etc., see charted treatment schedule on a preceding page

Suspensions in Oil for Injection—The two outstanding advantages of these preparations are that their injection causes much less pain than the injection of aqueous solutions, and the injections need be made only once a week in most instances. But to counterbalance these great advantages there are the following disadvantages: (a) Sterile abscesses of rather large propor-

tions may occur even a long time after the injections have been stopped, either they must be opened or they will spontaneously rupture, (b) Though embolism has occurred with perhaps no greater frequency than in the use of insoluble mercury, infarction following injection into an artery has been noted in a rather distressingly large number of instances—there is immediately great pain and nearly always ultimately gangrene and sloughing out of the affected area, (c) Occasionally during a period of very slow absorption a pocket of bismuth seems to empty quite suddenly into the circulation with a resultant explosive type of stomatitis. For a list of the chief preparations, dosage, etc., see charted treatment schedule on a preceding page.

Liposoluble Preparations for Injection—In the presence of certain lipid soluble substances, such as lecithin, matter may be satisfactorily dispersed in media in which it is otherwise insoluble. The first to make practical application of this fact to obtain optimal dispersion of bismuth were Hermann and Nathan, in 1925, in studies which have been continued by many other investigators. One of the chief advantages urged in favor of these liposoluble preparations is that they become effective, through rapid absorption almost as quickly as the water soluble salts and that their absorption continues almost but not quite as long as that of the insoluble salts. These claims seem to be borne out by careful excretion studies. The injections are further more, relatively painless and rarely lead to induration. Stomatitis probably occurs more often with these than with the water soluble preparations, but most of the cases are not severe. These liposoluble preparations are preferred by many of the leading Continental syphilologists, and latterly are gaining in favor in America because of their dosage being probably more exact than that of the oily suspensions and because they do not cause the late abscesses of these latter, and also because the therapeutic results obtainable with them approach closely those obtained by the use of water soluble preparations. Some of them are injected once some twice a week. For dosage, etc., see charted treatment schedule on a preceding page.

Intramuscular Administration of Bismuth—See the directions for injecting bismarsen on a preceding page.

Preparations for Oral Administration—For a number of years Hanzlik and his associates in San Francisco have been exhaustively studying the pharmacology of a substance, sobisminol mass, which is proposed for oral use in the treatment of syphilis whenever the employment of bismuth is indicated. We do not have any very complete clinical studies of the drug as yet and I was surprised when the Council on Pharmacy and Chemistry accepted it in 1939. Meisinger and Barnett (1939), of San Francisco, and Scholtz *et al* (1939), of Los Angeles have shown that sobisminol by mouth causes as rapid involution of the lesions in early syphilis as does bismuth injected intramuscularly, there were 90 cases in the one series and 32 in the other, but of course no leader in syphilology in America today is seriously proposing that the treatment of early infectious syphilis begin with bismuth instead of arsenic. With regard to sobisminol's use in continuous therapy in alternation with an arsenical there is nothing to say for no studies have been reported as yet. Meisinger and Barnett found it satisfactory in a combined scheme of therapy (see discussion of the 'combined' method on a preceding page) and feel it "certainly deserves further clinical trial." They thought that 2 capsules three times daily was optimal adult dosage (the

bismuth content of each capsule is 0.15 Gm.). The N N R dosage for children is 1 capsule three times daily and half this amount for a young child.

The drawback to this type of therapy is that it leaves the administration of the drug entirely up to the patient—to my mind a very objectionable and dangerous thing in the treatment of early syphilis. For patients compelled to be out of contact with their physician for a time it will probably find a useful place, but it is well to remember that even the most willing and intelligent individual will sometimes forget to take his "medicine," particularly when it must be done three times daily. No bismuth depot is established through oral therapy and the patient consequently has nothing to draw upon when he skips a few doses. In addition, we do not as yet know that assimilation of any given time does not depend upon the functional state of the gastro-intestinal tract at the moment.

Scholtz and his associates treated only 32 patients in early syphilis but a total of 90 in various stages of the disease. Of this number, some of whom received larger doses than the optimal of Meininger and Barnett, one or more reactions were experienced by 47. Seven complained of a bismuth line, 10 of stomatitis, 10 of grippe syndrome, 30 of nausea and vomiting, 11 of anorexia, 6 of diarrhea, 1 of dermatitis (questionable), 4 of urinary frequency, 2 of ptosis and parotitis, and 2 of esophageal spasm. Four had to discontinue treatment permanently and 7 temporarily. Most of the reactions occurred in the first few days or weeks on the therapy, most patients had no difficulties after the first two months.

Bismuth Reactions—Discussion of the several local reactions and injuries has been included in the above consideration of the three types of preparations introduced by injection. The reactions peculiar to the use of subbisminol by mouth have also been mentioned. In the matter of systemic reactions bismuth has the great advantage over both mercury and the arsenicals that, though the reactions of a toxic nature which accompany its use are many and varied, they are rarely severe enough when the injectable preparations are used to necessitate an interruption of the treatment for longer than a few days. The commonest of the symptoms is the appearance of a thin violaceous gray line on the gums, indicative of saturation. Another symptom of a deleterious nature which is relatively often noted (but not nearly so often as with mercury) is stomatitis, it is usually of a mild sort and disappears promptly upon adjustment of the treatment schedule or dosage. Experience has taught that it is well to examine the urine of patients before beginning the treatments and to use the findings as a quantitative guide to the same. Now and then during the courses the urine even of patients having no pre-existing nephritic disturbances will give evidence of a beginning toxic process in the kidneys, but this does not happen so often as with mercury and only rarely fails to disappear with adjustment in dosage or after a slight pause in treatment. According to Heilmann-Trosien (1928), in most instances the kidneys acquire an increased tolerance for the metal, but the fact is not established and is probably open to considerable doubt (Torvald, 1931). Very rarely indeed has a severe or long lasting nephritis or nephrosis been reported, but a few cases of anuria following a single injection are on record (the latest report is that of McClendon, 1941). Bismuth may induce diuresis and does so probably more markedly than and as often as mercury. Bismuth

induced Herxheimer reactions usually develop more slowly than those following arsenical medication

The following occurrences are relatively rare: loss of ambition, asthenia, headache, pains in bones and muscles, etc. (bismuth "grippe"), gastrointestinal disturbances, herpes zoster, purpura hemorrhagica, agranulocytosis, nitritoid crises, polyneuritis, various exanthemata and dermatoses (exfoliative dermatitis occurs and erythema of the ninth day has been seen twice by Goldman and Clarke 1930), pruritus, menstrual disturbances, etc. Prior to Wolman's (1910) report of 2 cases of acute yellow atrophy, both in infants ascribable to bismuth, no clear cut instances of this serious type of damage had been described. With the reactions of bismuth introduced intravenously we need not concern ourselves since the introduction of the drug by this route is absolutely contraindicated.

MERCURY IN THE TREATMENT OF EARLY SYPHILIS

The exhaustive comparative studies of mercurials, completed by Solimann, Cole and their associates in 1935, have excellently codified our knowledge of these drugs, but I do not feel justified in presenting a résumé of their work here at this time because mercury in all forms has now practically been abandoned in favor of bismuth. A few of the principal preparations are still included here (see below), but what needs to be said about them can be accomplished very briefly. (a) In early syphilis about the only justification for using mercury is if the patient is so isolated that during his heavy metal periods he cannot visit or be visited by the physician at short intervals for bismuth injections and the physician does not wish to entrust him with sublingual capsules to be taken by mouth. (b) Under these circumstances only the injection method of administration is feasible for mercury cannot be given intramuscularly through correspondence any more easily than bismuth, and the preparations available for oral administration are ineffective, often extremely irritating to the gastrointestinal tract, and very prone to cause severe stomatitis and profuse salivation. (c) The mercury course should not be any shorter than the preferable bismuth course would have been and it should if possible overlap the arsenical course at both ends, i.e., begin the use of mercury a week before arsenic is discontinued and extend it for a week after resuming the arsenical treatments—this is important to prevent neurorecurrence during the first course especially. (d) If both arsenic and the next best drug, bismuth, are felt to be contraindicated in the primary attack upon a given case of early syphilis as may very rarely happen, so that mercury has perforce to be used, the best procedure is to give daily intramuscular injections of either bimiodide or succinimide, next best, mercuric salicylate or the solution of colloidal mercury sulfide, either given intramuscularly twice weekly. (e) Mercury intravenously administered in early syphilis has made no place for itself as yet in this country. Mercury by inhalation and fumigation deserves no serious consideration. (f) Good care of the teeth and mouth probably aids considerably in preventing salivation. A mouth wash frequently used is the following:

R _x Tincture of kino	3j	30 0
Tincture of myrrh	3ij	60 0
Label: Add a few drops of the mixture to an ounce (30 cc) of water and use as mouth wash		

This mixture can be painted full strength on the gums if such special attention seems indicated

Mercury by Inunction—The preparation to use is the U S P "stronger mercurial ointment" which contains 50 per cent of mercury in a suitable base. This is not "blue ointment" which contains only 30 per cent of mercury and is therefore less effective, nor is it "calomel ointment," which has no antisyphilitic value whatsoever. A dose of about 1 drachm (4 Gm) is rubbed for thirty minutes into a different hairless portion of the body on each of six consecutive days, the site of inunction being previously washed with soap and water and then alcohol. A full bath with soap and water, but no rub, comprises treatment on the seventh day, on the next day the second course of rubs begins. This is a very effective way of mercurializing a patient but it is difficult to get him to persist in the timed rubs and the procedure is a very dirty one and not easy to conceal from family and associates. A very simple method of cleansing the skin after an inunction is to wipe off the excess ointment with benzine or naphtha or very quickly with a good grade of leadless gasoline. In their earlier reports Cole and Sollmann stated that this cleansing does not lessen the effectiveness of the treatment, but in their later studies it seems that they have not entirely confirmed this impression. The United States Public Health Service has employed a belt or girdle on which the ointment is smeared. Dermatitis of various sorts may arise and cause temporary cessation of treatment but it is doubtful if absorption is affected by the skin disturbance. Massive inunction, in which nearly the entire body surface is rubbed once a week with 1 ounce (30 Gm) of the 30 per cent ointment, is a feasible substitute for the daily rubs but hardly of any practical importance for the general practitioner.

Mercury by Intramuscular Injection—For the practitioner who must occasionally inject mercury, the following 4 preparations will probably meet all needs. Both the *bimiodide* (*red mercuric iodide*) and the *succinimide* are available in commercial ampules containing the adult dose $\frac{1}{2}$ grain (0.01 Gm). The injection is usually given cold and is often sharply but briefly painful. *Solution colloidal mercury sulfide* is usually given twice weekly in adult dosage of 2 to 3 cc. The injection seems to be quite painless but sometimes an unsightly though harmless discoloration remains under the skin. *Mercuric salicylate* is commercially available in ampules containing 1, 1½ and 2 grains (0.06, 0.09 and 0.12 Gm) of the salt suspended in oils. The ampule must be immersed in warm water to liquefy its contents before use. Injections are usually made weekly and are rarely very painful at the time but there is not infrequently considerable and long lasting pain which begins later. The adult dose is 1 to 3 grains (0.06–0.12 Gm), Stokes says that less than 2 grains (0.12 Gm) is almost certainly ineffective. Mercuric salicylate is slowly and irregularly absorbed and probably a considerable part of it is eliminated unchanged and without having exerted mercury effect, the only advantage which it possesses, in addition to being usually relatively painless at the time of injection, is that it is given less frequently than the other preparations.

Serious local reactions which may follow intramuscular injection of either mercury or bismuth are discussed under the bismuth preparations on a preceding page, and directions for correct intramuscular injection will be found under the discussion of bismarsen among the arsenicals.

Mercury by Mouth—Inadvisable to use in early syphilis, the preparations are listed here merely because in the discussion of latent syphilis the reader is referred to this place for such a list. *Yellow Mercurous Iodide (Protoiodide)* The adult dose ranges from $\frac{1}{2}$ to 1 grain (0.01–0.06 Gm), three times daily in tablet form, the average tolerated dose is perhaps about $\frac{1}{2}$ grain (0.015 Gm). *Mercury with Chalk (Gray Powder)* Dose 1 to 4 grains (0.06–0.24 Gm), three times daily in capsules, or the sweet powder may be taken as such. *Mercuric Chloride (Bichloride)* Dose $\frac{1}{20}$ to $\frac{1}{2}$ grain (0.003–0.015 Gm), three times daily. In my time at the New York Skin and Cancer Hospital this drug was combined with iodides in the following prescription for "mixed treatment", the iron and strychnine are present in the hope of combating the anemia and anorexia that are frequently very prominent features in individuals being dosed with mercury (see below)

R̄	Mercuric chloride	gr	iss	0	00
	Potassium iodide	ʒ	iv	16	0
	Ferric and ammonium citrate	ʒ	ij	8	0
	Tincture of nuxvomica	ʒ	ij	8	0
	Water to make	ʒ	iv	128	0

This preparation, which contains approximately $\frac{1}{20}$ grain (0.003 Gm) of mercuric chloride and 8 grains (0.5 Gm) of potassium iodide to the teaspoonful, may be given in 1, or cautiously 2 teaspoonful doses three or four times daily. *Red Mercuric Iodide (Biniodide)* This preparation may be dispensed in a bottle when rendered soluble by adding an equal quantity of sodium or potassium iodide. The tolerated dose ranges between $\frac{1}{20}$ and $\frac{1}{2}$ grain (0.003–0.02 Gm), most patients can be safely started on $\frac{1}{10}$ grain (0.006 Gm).

Systemic Reactions to Mercury—(a) Diuresis, occurring somewhat less frequently than with bismuth. (b) Renal disturbance of nephrotic nature, more frequent and severe than with bismuth. (c) Gastrointestinal disturbances even from preparations not administered by mouth: anorexia, salivation, stomatitis, colic and intractable diarrhea. (d) Anemia, wasting, polyneuritis, depression (even in occasional psychosis). (e) Rheumatism, more severe than the "grippe" of bismuth. (f) Cutaneous reactions, other than the local disturbances associated withunction are rare.

TREATMENT OUTLINES FOR EARLY SYPHILIS

Now for the important questions: How long must active and continuous treatment last? During this period how much arsenic and how much bismuth? How space and how alternate the drugs? How much serologic testing and when? What are the real criteria of "cure"? When may the syphilitic marry?

Length of Treatment—Since there is no method known today by which an exceptionally responsive person can be recognized when treatment is begun or during its progress, the only defensible method is to treat every patient as though he belonged to the group which is most resistant to treatment. In the findings of the Cooperative Clinical Group it appears that such a patient, if the infection is diagnosed in the seronegative primary stage, if he is fully cooperative, if treatment is begun at once and continued uninterrupted and without complications, can be nearly certain of being cured in

twelve months. If the diagnosis is not made until the seropositive primary or early secondary stage, with all other conditions remaining the same, the cure will require eighteen months and is not quite so certain of being achieved (the criteria of "cure" are discussed later).

Total Amounts of Arsenic and Bismuth—The Group studies show that the seronegative primary patient, who may expect to complete his cure in twelve months if all goes well, should receive a minimum of 30 doses of arsenic and the same amount of heavy metal. In terms of the actual drugs and methods available for the use of the general practitioner, this means the giving of 30 intravenous injections of neoarsphenamine or mapharsen and about the same number (or more, depending on the preparation used) of intramuscular injections of bismuth, or if bismarsen is being used, 60 intramuscular injections of that drug. The seropositive primary or early secondary patient, who must be treated for eighteen months, will have to continue the treatment until he has received half as much again of both arsenic and bismuth. Dosage, etc., will be found in the charted treatment schedule on a preceding page.

Spacing and Alternating the Drugs—Syphilologists are not always in agreement among themselves and I have not found any satisfactory and authoritative published schedule of treatments based primarily upon the use of the private practitioner's drugs—neoarsphenamine and bismuth, with mapharsen and bismarsen also worked into the scheme to give some choice of arsenicals. I believe the following to be both safe and practical for the general man, though I am not unaware that these terms, especially "safe," may be assailed from almost as many standpoints as there are predilections among the specialists.

As stated earlier in the article, the attack should be begun with an arsenical. If neoarsphenamine is being used, the first 4 injections may well be given on the first, fifth, tenth and fifteenth days respectively. This will end the first two weeks of treatment, and thereafter an injection should be given once each week until a total of 12 has been administered. In the last two weeks of this arsenic course the intramuscular injection of bismuth should begin, the number of injections in this period depending upon whether a preparation suitable for weekly, biweekly, or triweekly administration is chosen. Overlapping of this sort is especially important here in this first course in the attempt to prevent neurorecurrence. Then when the last of the arsenic is given the bismuth injections are continued alone until eight weeks (or slightly less if certain of the preparations are used) of bismuth therapy has elapsed. During the last two weeks of this bismuth course weekly injection of arsenic should have been resumed, and then the arsenic is continued alone until 10 weekly injections have been given. Succeeding this and always overlapping two weeks at each end, there will be another ten weeks of bismuth, ten weeks of arsenic, and a final ten weeks of bismuth. This point will be reached in about twelve months (forty-eight weeks to be precise), and if all has gone well the patient in whom treatment began in the seronegative primary stage may now be placed on probation, for the seropositive primary or early secondary patient, another ten weeks of arsenic, ten weeks of bismuth, ten weeks of arsenic, and a final ten weeks of bismuth will be required to complete his approximately eighteen months (eighty weeks actually) of treatment. These details are displayed in a simple form

in the charted treatment schedule on a preceding page. If hismarsen is being used of course no alternation can take place since arsenic and hismuth are combined in the one preparation, the drug is merely injected weekly, or perhaps better twice weekly if it can be borne, without intermissions until the total number of doses has been given.

With Which Drug to End the Treatment?—The point is well established by experience that it is better to end with a hismuth (or mercury) course than with an arsenical.

Serologic Testing During Treatment—I quote Moore (1936), the Johns Hopkins member of the Cooperative Clinical Group: "The duration of treatment may be measured if desired, though preferably only by the expert by serologic standards. On this basis, the criterion set by Keidel 20 years ago still holds good, namely, one full year of continuous treatment after serologic tests of blood and cerebrospinal fluid have become and have remained completely negative. Since the use of such a standard demands frequent repetition of serologic tests, thereby adding to the cost of treatment, and since difficulties of interpretation of such serial serologic testing confront both the inexperienced physician and his anxious patient, it is probably better for the average practitioner to discard the serologic method of treatment control and to rely on the arbitrary standard already mentioned. These standards, i. e., 12 months of continuous treatment for seronegative primary syphilis and 18 months of continuous treatment for seropositive primary or early secondary syphilis are in fact based upon the correlation of clinical and serologic standards in thousands of patients treated under expert control."

The Criteria of "Cure"—If the patient has satisfactorily completed a standard treatment as above outlined he may be considered probably cured if he satisfies the following requirements: (a) Negative blood and spinal fluid at end of the treatment. (b) A full year of probation during which he receives no treatment, develops no lesions of syphilis and maintains a steadily negative blood, the latter to be determined by serologic tests performed at frequent intervals but certainly no less often than every three months. (c) At the end of the year a complete examination, which must be negative for evidences of progress in the disease, especially in the nervous system or cardiovascular apparatus, evidenced in the former by freedom from neurologic signs with a negative spinal fluid and in the latter by negative findings upon both physical and roentgenologic cardiovascular examinations. (d) Annual repetition of the complete examination as above except that if the second spinal fluid examination is negative this test need not be routinely repeated in the subsequent years.

Marriage—From the immediately preceding statements it will be seen that "cure" is merely a facile term for unremitting watchfulness. People have contracted syphilis from individuals who had neither clinical nor serologic evidences of the disease. Nor is the fact of adequate treatment always a guarantee of protection, Lunsford and Day (1934) infected rabbits by lymph node tissue transplantation from 3 patients who had received continuous and intensive treatment from the beginning of their infection and for periods of eighteen, thirty, and thirty six months, respectively.

Therefore the physician can never guarantee that a patient is completely noninfectious. Can the young syphilitic, healthy save for his infection, never marry then? He is going to do so of course, but when may this take place

with greatest safety for his wife and future children? The most lenient of all the answers to this question provided by those who can speak authoritatively is that of Moore (1933) "Sexual intercourse is permitted after the sixth month of treatment provided that (a) the patient wears a condom and (b) that intercourse occurs during the arsphenamine phase of therapy. As to marriage and unrestricted sexual intercourse continuous treatment for 12 to 18 months, during the last year of which the patient is seronegative, after which marriage may be permitted." On the basis of their study of conjugal syphilis at the Mayo Clinic, and writing of syphilis *per se* without any relationship to the amount of treatment received, O'Leary and Williams (1940) say the disease may be considered to be infectious during the first five years but that each year thereafter the possibility of the individual transmitting it decreases until it approaches a vanishing point by the tenth year.

TREATMENT OF "TREATMENT RESISTANT" SYPHILIS

The truly treatment resistant syphilitic is one in whom either spirochetes' lesions or serologic manifestations or all three are not typically affected by correct antisyphilitic therapy. The arsenicals are the drugs against which resistance is most often manifested, and most of the patients are early syphilitics, though resistance may be encountered in any stage of the disease. Apparently arsphenamine resistant syphilis is increasing in both Germany and France; the excellent review of Beerman (1936) indicates that no such increase has occurred in the United States. In the American cases recently described by Netherton (1937), and Beckh and Kulchar (1939), it did not seem that the trouble could be ascribed to infection with a treatment resistant strain of organism. The latter authors feel that most of these resistant cases are seen in patients who have been treated with some form of "combined" therapy as discussed in the preceding pages.

In the matter of therapy it seems to me that when the general practitioner encounters one of these rare cases the best thing he can do in the interest of his patient is transfer him to the practice of a competent syphilologist, for the measures usually employed in attempting to alter the response in such a case call for special training, experience, and equipment. The chief of these measures are (a) Running the gamut of the arsenicals (b) Use of bismuth and mercury and perhaps such minor drugs as gold salts and sodium thiosulfate (c) Temporary suspension of all treatment under expert and constant supervision (d) Shock and fever therapy.

TREATMENT OF LATENT AND WASSERMANN FAST SYPHILIS

In this section we will be concerned with a certain type of patient recruited from the following classes: (1) those whose early syphilis was ignorantly or wilfully not treated at all, (2) those whose early syphilis was inadequately treated, and (3) those in whom lesions of the primary and secondary stages were wholly absent or so slight and transient that opportunities for diagnosis and treatment did not present themselves. But not all individuals who for one reason or another did not obtain satisfactory treatment of their acquired syphilis fall within the present category, for a certain number of them will have earlier presented themselves with one or more of the lesions of late syphilis. The group is therefore whittled down to include only those

patients whose sole manifestation of the disease is a positive blood Wassermann or Kahn reaction, such individuals are said to have "latent" syphilis. But be sure the reaction is not falsely positive, in addition to a large number of diseases in which it is not yet possible to estimate the incidence of transitory false positive reactions, Moore *et al* (1940) say the probable frequency in yaws is 100 per cent, leprosy 40 to 80 per cent, malaria 100 per cent at some time during the infection, and infectious mononucleosis 20 per cent.

Now what to do when a patient with true latent syphilis is detected? In the first place the thing *not* to do is plunge in, hurly burly, to "clean him up" with intensive chemotherapy, for to do this may cause irreparable damage. The really proper lines of action I shall attempt to present briefly in what follows.

Search for Hidden Syphilis—The patient should be thoroughly examined, with ophthalmologic, roentgenologic and other help as needed from specialists, to bring from below the subclinical level any occult syphilitic lesions which may be present. At once these are found the therapeutic interest shifts to them and the Wassermann reaction merely becomes one of the several parts of the picture. Neurosyphilis, cardiovascular syphilis, hepatic, gastric, osseous, and other miscellaneous manifestations of late syphilis are all discussed in sections of their own. These very serious cases disposed of through proper classification, which brings with it automatically the correct type of treatment, we must then decide for those which still remain in the latent class whether to treat them at all or not.

Course of Untreated Latent Syphilis—If at the time of the diagnosis of latency the disease has existed four years so that the patient's own defensive mechanism has already become firmly established, the Cooperative Clinical Group finds that the untreated course will be about as follows: (a) Ultimate spontaneous "cure" (negative blood and spinal Wassermann, no lesions), 25 to 35 per cent of patients; (b) Infection remains latent (positive blood but negative spinal fluid, no lesions), 25 to 35 per cent; (c) Late cutaneous, mucosal or osseous syphilis, 10 to 15 per cent; (d) Cardiovascular syphilis, 10 to 15 per cent; (e) Neurosyphilis, 1 to 2 per cent; (f) Other visceral syphilis, 1 per cent or less. Repeated in other words this means that even if left absolutely untreated 50 to 70 per cent of the patients (always with the proviso that their syphilis is four years old when latency is diagnosed) will grow no worse and about half of that proportion will actually achieve spontaneous "cure", while about 20 to 30 per cent will develop visceral, cardiovascular, or some other form of late syphilis, and 1 to 2 per cent will eventually have neurosyphilis.

Course of Treated Latent Syphilis—By proper treatment, the Group found it possible to achieve in 55 to 60 per cent of cases a result comparable to the spontaneous "cure" achieved in only 25 to 35 per cent of untreated cases, though it is admitted that unavoidable statistical errors may have allowed this figure to transcend the truth somewhat. But even so, it is apparent that an appreciably greater proportion of individuals with true latent syphilis will get rid of their infection if correctly treated than if left untreated.

Whom to Treat—I must repeat here, since it is so important for the reader to bear in mind, that in all of this discussion we are concerning ourselves only with true latency, *i e*, individuals in whom the most searching

examinations have failed to detect any evidence of the disease other than the positive blood Wassermann reaction. Such patients are divisible into 2 groups 'early' latency, with the full defense mechanism not yet established since the infection is less than four years old, and 'late' latency, in which the patient has had time to develop completely his spontaneous resistance. It seems that practically always in "early" latency treatment should be instituted for the reason that such patients, being usually still quite young and sexually active, are a social menace through their still considerable likelihood to develop infectious relapse, furthermore, the fact that they are not far removed in years from what was probably wholly inadequate arsenical treatment means that the occurrence of precocious tertiarism may still be expected in them. But in 'late' latency the decision to treat or not to treat is more a matter of expediency. The studies of the Group reveal that the liability of a truly latent individual (*i.e.*, with a negative spinal fluid when the diagnosis is made) to develop neurosyphilis is extremely small. Also if ten years have elapsed since infection and no evidences of cardiovascular involvement are found when the diagnosis of true latency is made, then such involvement is fairly certain not to occur later—though Stokes' reminder is an important one, namely, that the state of the small arteries of the brain, of the myocardium, and the coronary system is extremely difficult to appraise. It is clearly the opinion of Moore and of Stokes, and very probably of all the other outstanding syphilologists who comprise the Group, that an individual who is over fifty years of age, whose infection is of long standing and gives no more evidence of its existence than the positive blood Wassermann and a scar or two, such as a fixed pupil or an absent knee jerk—that such an individual is best left undisturbed by treatment, to come to death from causes other than his syphilis (Mercury by mouth, or 'mixed treatment' with mercury and iodides, has been much used in the past in such cases, but I believe that this kind of therapy might well be dispensed with entirely in our day). In individuals younger than this each case must more definitely be weighed on its own merits. Stokes believes that the patient in his thirties or forties may still have time to 'use up' all of his immunity and he therefore advocates treatment in all these cases. It is certainly true that some crippling degenerative process coming on many years after the primary infection may find such a patient still in his 'best' years.

How to Treat.—The findings of the Group indicate that for "early" latency the best plan is to treat continuously for a year, or arbitrarily for two years if Wassermann fastness occurs and that the amount of arsenic may well be curtailed in favor of more heavy metal. Many observers, such as Stokes, believe that the course should begin with heavy metal to safeguard the patient against serious Herxheimer reaction in a lesion which the exercise of our utmost diagnostic acumen has failed to reveal, it should also end with heavy metal. I think that these requirements will about be filled by giving within the year 3 bismuth courses of 12 weekly injections each alternating with 2 arsenical courses of 8 weekly injections each overlapping the drugs for one week at each end. Or perhaps the bismuth courses may be made even longer than this at the expense of arsenic. Rein and Wise (1939) conclude from a large experience that mapharsen is the arsenical to be preferred in latency because of its relatively lower toxicity, this is certainly the consensus nowadays. If the reader will turn to the charted scheme

for the treatment of early syphilis on a preceding page he will find that a course of therapy for latent syphilis can be laid out very easily by omitting the first arsenical course on that chart and proceeding from that point merely to lengthen the bismuth and shorten the arsenical courses as much as is desired.

The above plan is for "early" latency, be it noted, in "late" latency the Group has found that the necessity for continuous treatment is not so imperative. Rest periods in these cases seem to do no harm. Likewise it seems sometimes to be of value to use a little mercury in some of the patients, preparations and methods are described in the discussion of mercury in the treatment of early syphilis.

Wassermann "Fastness"—From what has been said in this section I imagine it is apparent that the mere fact of a persistently positive blood Wassermann reaction is in itself not of fundamental significance. Some of these reactions are undoubtedly due to the refinements in present-day serologic methods, some of them disappear spontaneously several months after cessation of treatments, some of them are increased in positiveness and possibly more firmly "fixed" by treatment. The thing of chief importance is to see that the latency itself, and not the Wassermann fastness is assessed at its proper value and treated or not accordingly. If in a given case there seems to be reason for attacking the fastness alone, the other indications having been satisfactorily met by treatment, then it seems to me that the general practitioner is well advised to turn his patient over to a specialist who will likely attempt some such juggling as is employed in combating arsenic resistance previously discussed.

TREATMENT OF EARLY NEUROSYPHILIS

Almost certainly the best that the general practitioner can do to safeguard his patient against the development of neurosyphilis at any time is to treat him most vigorously during his early syphilis according to some such plan as that presented in this book. Primary acute syphilitic meningitis, with any or all of the following symptoms, is of extremely rare occurrence under such conditions, and can be taken to mean that the individual is not being treated with enough intensity: headache, pain and stiffness in the neck, nausea and vomiting, mental signs, convulsions, cranial nerve palsies, anhalasia, hemiplegia, increased cerebrospinal pressure, pleocytosis and a positive Wassermann of the fluid. Such an occurrence calls for hospitalization and intensification of the chemotherapeutic attack for several weeks. Such intensification can be accomplished by modifying the scheme in the charted treatment outline on a preceding page so that the arsenical is given at five day intervals and the bismuth preparations used at the same time. After the symptoms clear up the routine treatments can be resumed. Merritt and Moore (1935) find it of value during the acute period to drain off spinal fluid repeatedly until the fluid circulation is readjusted. Failure to respond to such intensification of course necessitates resort to tryparsamide, intraspinal or fever therapy.

The occurrence of such a syndrome as the above in the form of a true neurorecurrence, *i.e.*, the "lighting up" of dormant neurosyphilis during a lapse in treatment, will not be seen during the proper treatment of acute syphilis if the patient is cooperative. Precocious tertiarism, which may involve

the nervous system, will also not be seen if the patient is being adequately treated

The primary problem for the practitioner, then, is to see to it that his patient with early syphilis receives at least as vigorous therapy as is outlined in this book and that at the end of the first year of treatment an examination of the spinal fluid is made. If the findings are negative, the blood Wassermann is negative, and treatment was begun in the seronegative primary stage, the patient is ready for probation (but this will be true only after another six months of treatment if diagnosis was not made until the seropositive primary or early secondary stage). At the end of the year of probation, another spinal fluid examination, and if it is also negative the patient may be assured with fair certainty that he will not subsequently develop neurosyphilis. But what to do if one of these spinal fluid examinations is positive? Be guided by the serologist's interpretation, seems good advice if the Wassermann is only mildly positive and there are none of the other alterations in the fluid by which "paresis sine paresi" is diagnosed, mere continuation of the treatment with intensification will probably suffice, though only if treatment has not been already stopped. That is to say, if the fluid is mildly positive before probation begins merely continue the treatment with intensification, if "paresis sine paresi" is made out in the fluid, or if the mild positive turns up only after probation, then it is certainly best to approach the case as one of late neurosyphilis and treat accordingly (see below). And to have expert advice through consultation with a syphilologist is certainly the part of wisdom.

TREATMENT OF LATE NEUROSYPHILIS

As late neurosyphilis I am considering here the occurrence of any of the following in a patient having latent syphilis: paresis and taboparesis, tabes dorsalis, optic atrophy, and meningo-vascular (cerebrospinal) neurosyphilis including such widely separated entities as transverse myelitis, syphilitic epilepsy, brain gumma, late syphilitic hemiplegia combined symptom disease, and late asymptomatic neurosyphilis. The guiding principles of treatment will be supplemented by details of application of those measures only which can be feasibly employed by the nonspecialist.

Importance of Preparatory Treatment with Heavy Metals and Iodides Before Beginning Use of Arsenic—All authorities are in agreement upon the advisability of beginning treatment with a heavy metal, some are clinging to mercury still but undoubtedly bismuth has replaced the older drug in most practices even in the treatment of neurosyphilis. Iodide is hallowed by usage at least and is probably of value. When arsenic is added later it should be given as intensively as possible. To accomplish these things, the charted treatment outline on a preceding page may be altered as follows: (a) Begin with a ten weeks' course of bismuth injected weekly, or perhaps preferably, an eight weeks' course using preparations which may be injected twice or thrice per week. (b) Add arsenic in the last two weeks, injecting every five days if possible for a course of 10 injections. (c) The bismuth should overlap the arsenic again at the end or it may be possible to continue it in half dosage throughout the arsenic period. (d) Give 3 to 5 such courses (one round of bismuth and arsenic constituting a course) and taking care to end with bismuth just as the beginning was made with bismuth. (e) Use iodides throughout, according to methods discussed on a later page.

The University of Chicago group (Walsh and Becker, 1941), whose favoring of "combined" bismuth and arsenic therapy has been referred to under treatment methods for early syphilis are particularly pleased with their results in neurosyphilis with a routine about as follows: Five weeks of daily intramuscular injection of a soluble bismuth preparation together with daily intravenous administration of 25 to 100 cc of 10 per cent sodium iodide solution (alternately, weekly injections of insoluble bismuth and iodides daily by mouth), four weeks' rest, six weeks of arsenic and bismuth simultaneously, four weeks' rest, eight weeks of bismuth, four weeks' rest, six weeks of arsenic and bismuth, four weeks' rest, eight weeks of bismuth, four weeks' rest, six weeks of arsenic and bismuth. What pleases them in their results is that they feel they were attained with less frequent resort to tryparsamide, intraspinal or fever therapy than is necessary in the Cooperative Clinical Group methods outlined above. Of course time alone will tell which of these types of approach is the better.

In choosing a bismuth preparation in neurosyphilis it has been thought on the basis of the studies of Hanzlik and associates (1932-1935), that perhaps iodobismutol-with saligenin might effect better penetration of nervous tissues than other preparations. It is difficult to put such things to adequate clinical test, however, as shown by the recent studies of Kulehar *et al* (1940), and it therefore seems that no one bismuth preparation has yet been shown with certainty to be the superior of any other.

As in latent syphilis so also here, a lapse in treatment is not so serious a thing as it is in the treatment of early syphilis, still, continuous treatment—no intermissions between courses—is preferable, at least in the Group type of treatment, and should be insisted upon.

It is well to remember that Herxheimer reaction, with its typical intensification of symptoms, does even occur with bismuth therapy.

Intensification of Treatment by Use of Tryparsamide, Intraspinal Treatment, or Fever Therapy—Some cases of neurosyphilis can undoubtedly be arrested if not actually cured by one or the other of the types of treatment discussed above, such treatment should certainly be given the preference in all patients seen early except perhaps in fulminating cases of paresis or taboparesis, or in optic atrophy. Still, in all types of late neurosyphilis in all stages the newer methods are challenging these older ones in unmistakable fashion, the decision when to turn to them will certainly not be an easy one for the practitioner to make. However, if his patient is only mildly affected and is being held stationary by treatment, I should think that the danger to eyesight in the use of tryparsamide and to life itself in the fever methods might give him pause. The largest available authoritative statistical analysis is that of Hopkins, who, in 1933, reviewed the results in 1200 patients at the Johns Hopkins Hospital, with the following findings: (a) Intensified routine antisyphilitic treatment was best in early neurosyphilis. (b) In paresis and taboparesis, malaria was preeminently the treatment of choice. (c) In tabes, malaria was best, tryparsamide almost as good, and either one far superior to routine therapy. (d) In meningovascular (cerebrospinal) cases, intraspinal therapy and tryparsamide were superior to malaria, routine treatment was much inferior to any of these methods. (e) In optic atrophy, subdural injections of arsphenaminized serum (Swift Ellis intraspinal therapy) arrested the process in numerous cases in which it was advancing in spite of routine methods.

of treatment. Woods and Moore of this same hospital, definitely advised many years ago against tryparsamide, which they and many others consider contraindicated in optic atrophy.

More recently than the above Moore *et al* (1938) have discussed the treatment of optic atrophy and reached conclusions which may be summarized as follows (1) Untreated primary optic atrophy always becomes bilateral and practically always leads to permanent and complete blindness in seven years (2) Adequate routine therapy delays the process and in an occasional case arrests it. (3) Subdural (Swift Ellis) treatment arrests the process in about 50 per cent of instances, though it carries the risk of sudden extinguishment of vision in about 10 per cent of those treated (4) Malaria therapy brings about permanent arrest more frequently than subdural therapy, and therefore, and because it is less dangerous to vision than subdural therapy, it is the preferred initial form of treatment. (5) If visual failure progresses in spite of malaria, subdural therapy should always be tried (6) Either of these forms of therapy should be followed by intensive routine antisyphilitic treatment.

Bennett *et al* (1930) find that in all types of active clinical neurosyphilis the simultaneous employment of fever therapy and chemotherapy is preferable to fever therapy alone, but it will probably take a very thorough alternate-case type of study to prove or disprove the point. Ciocco and Weinstein (1934) were obliged to report that no type of antisyphilitic therapy affects deafness in late syphilis either favorably or adversely.

Fever Therapy.—Since Wagner-Juregg's introduction of malaria therapy, in 1918, this original form of fever therapy has been extensively used throughout the world. Later proposals to replace malaria with relapsing fever or rat bite fever did not meet with ultimate approval because these agents failed to prove their superiority. However, in recent times, the supremacy of malaria is being staunchly challenged by various physical methods of inducing fever: diathermy, short wave radiotherapy, conditioned hot air cabinets (hypertherm), hot baths, infra red radiation. Each of these new methods is being advocated almost with cultist fervor by its devotees, though the actual improvement which any of them effects over the classical malaria treatment is probably not proved. But it is certainly not for me to say, what has been clearly shown, however, is that all of these physical methods, as well as malaria, require specially trained staffs for their successful use with the minimum of danger. When the general practitioner has a candidate for fever therapy the best he can do is to turn him over to the ministrations of a department in a hospital where malaria or one or other of the physical methods is being frequently used. Blanket wrapping, one of the latest departures among the physical methods, may perhaps be suitable for use by the general practitioner, I shall describe it below. A number of nonspecific chemical and biologic products have also been used: typhoid vaccine, gonococcus vaccine, milk, sulfur, peptone, turpentine, sodium nucleinate, blood (autohemotherapy). Of these, the only one which has acquired any sort of lasting status is typhoid vaccine, and since it may be applicable to the general practitioner's needs, the technic will be described here.

Blanket Wrapping.—Epstein and Cohen (1935) have introduced this method, but in doing so they stress the necessity of careful nursing attention throughout the treatment. I therefore describe it not as a method which

can be haphazardly applied in the home, but as one which is available to the practitioner who can use it with no more specialized assistance than will be available in the average first-class hospital. No special preparation is necessary and the patient may have his breakfast. Wearing long woolen socks over the feet and legs he gets into a bed on which have been placed first a large rubber sheet, then a large canvas sheet, and on top so that the patient will lie directly on it, a heavy woolen blanket. As he lies on his back each limb, the trunk and the shoulders are wrapped individually with warm, thin bath blankets. Then the entire body is wrapped in a bath blanket, with only the face protruding, 7 bath blankets are used in all. Last, the heavy blanket, canvas sheet and rubber sheet (extra large so as to cover the whole pile) are drawn around the patient, the whole bundle is wrapped in another heavy woolen blanket and a last one is placed over the lower part of the body. The oral temperature and pulse at the temple are taken at half hour intervals and after each reading the patient takes through a tube 100 cc of hot (100° F) lemonade containing 0.0 per cent sodium chloride and sugar to taste. A temperature of 102.2° F (39° C) is usually reached in three or four hours and 104° F (40° C) in five to six hours, it is maintained between 104° F (40° C) and 104.9° F (40.5° C) for the six hours which usually constitute a treatment. A rapid rise of temperature above this latter point should be controlled by loosening the blankets, fanning the body, administering cool drinks, and, if the condition is alarming by a cool colonic flush. The pulse rarely exceeds 140 and the respiratory rate 28 per minute. A pulse rate above 150, a fall in systolic blood pressure below 80 mm of mercury, tendency to collapse, or the onset of tetany are indications for discontinuing the treatment. When the fever reaches its height restlessness may be controlled by hypodermic injection of morphine sulfate $\frac{1}{4}$ grain (0.015 Gm) and atropine sulfate 1/150 grain (0.0004 Gm), after which the patient may sleep. Treatment is not given to patients of advanced age those with serious cardiac or pulmonary disease or with a severe degree of arterio-sclerosis and the course of weekly treatments is discontinued during acute upper respiratory infection.

Typhoid Vaccine—This method seems to be the only other one (see blanket wrapping above) available for application by the general practitioner himself, but it too requires careful and constant observation of the patient, oftentimes the reactions are very sharp and severe. The typhoid vaccine method has the same contraindications as blanket wrapping which should probably take precedence over it for the general practitioner. One cc of commercial typhoid vaccine containing 1,000,000,000 organisms is diluted to 10 cc with physiologic saline solution and kept in the refrigerator for use throughout the series of 10 to 16 reactions treatments being usually given on alternate days. Using a tuberculin syringe for accuracy, doses of 10,000,000 or 15,000,000 organisms are given for the first 4 or 5 treatments and usually 15,000,000 or 20,000,000 for subsequent ones. The Nelson technic of giving a second injection at the height of the fever produced by the first is the one most usually employed. The first intravenous injection is given in the morning, the patient usually experiencing a chill within thirty minutes to two hours thereafter, this lasts for a few minutes and is followed by a rise of temperature. When the rise is well established and progressing the second intravenous injection, using the same dosage, is given. The interval between

the 2 doses should not be less than two hours, Driver and Shaw (1933) found that a three- to six-hour interval is equally satisfactory, provided the temperature has not dropped to nearly normal by this time. Temperatures of 105° F (40.56° C) to 107° F (41.67° C) are usually obtained by this method.

Tryparsamide—The drug is usually given intravenously in a dose of 30 to 50 mg per kilogram (2.2 pounds) of body weight, the average adult dose of about 3 Gm is dissolved in the ampule in 10 cc of sterile, distilled water, and given at weekly intervals for eight to sixteen weeks, followed by a rest period of about six weeks. Many such courses are usually necessary to accomplish full results. The drug may also be given intramuscularly or subcutaneously, though it is often quite irritating under these conditions. Tryparsamide solutions should not be sterilized as this will cause an increase in toxicity, and the solution should be injected as soon as it is prepared. It is usual to give bismuth during the rest period. A fact which is being somewhat overlooked at present is that Lorenz *et al* pointed out that their results were better when they gave 1 cc of mercuric salicylate intramuscularly three days before each tryparsamide injection, some physicians are now giving full doses of either mercury or bismuth throughout the tryparsamide courses.

Nearly all patients gain considerably in weight and well being while taking the drug. Until recent years the most frequent complaint was of ringing in the ears and a feeling of being dizzy and dazed. Nitritoid reactions, nausea, vomiting, and headache were of comparatively rare occurrence, and urticarial reactions, dermatitis and jaundice had been reported only a few times. But at the present time the drug seems to be producing constitutional reactions more frequently than formerly, the reason for this change is unknown but it is reported that the manufacturers have become concerned about it, very probably the cause of the alteration in toxicity will soon be found. It appears that tryparsamide also occasionally activates mental and physical signs and symptoms in a most objectionable way.

Visual disturbances occur with sufficient frequency under tryparsamide therapy that the drug should be used only with the greatest care. Patients with preexisting optic involvement, such as contracted fields or abnormal fundi, are more liable to injury than normal patients, but since some of these patients experience a great improvement in their vision under treatment with the drug, its routine withholding in these cases is not warranted, though in such cases there should be expert ophthalmologic, and if possible syphilologic supervision (and see the preceding summary of Moore's conclusions regarding the therapy of optic atrophy). The most important signs of adverse action of the drug on the optic tract are subjective dimness of vision, flickering or shimmering sensations, or flashes of light, also objective diminution in the visual acuity, contraction of the visual fields and changes in the fundi. The occurrence of subjective symptoms should be thoroughly investigated for an objective basis. If no objective signs are found, tryparsamide may be continued with caution. The presence of objective findings, traceable to the drug, is a contraindication to its further use for at least a month, after which it may be very cautiously resumed—but I repeat, this should all be done only with the most expert consultation available.

Swift-Ellis Intraspinal Technic.—One-half to one hour after intravenous

injection of an arsenical 40 cc of blood are withdrawn into bottle-shaped centrifuge tubes allowed to coagulate centrifuged and placed in refrigerator The following day 12 cc of this serum are diluted with 18 cc of normal saline and heated at 56° C for one-half hour After lumbar puncture the cerebrospinal fluid is withdrawn until the pressure is reduced to 30 mm The barrel of a 20-cc Luer syringe (which has a capacity of about 30 cc) is connected to the needle by means of a rubber tube about 40 cm long The tubing is then allowed to fill with cerebrospinal fluid so that no air will be injected The serum is then poured into the syringe and allowed to flow slowly into the subarachnoid space by means of gravity Usually the serum flows in easily under even a lower pressure but at times it is necessary to insert the plunger of the syringe to inject the last 5 cc By the gravity method the danger of suddenly increasing the intraspinal pressure to the danger point such as might occur with rapid injection with a syringe is avoided Pain in the legs commencing a few hours after the injection is more often noticed in tabetics than in patients with cerebrospinal syphilis It can usually be controlled by means of phenacetin and codeine but occasionally morphine or dilaudid is required

Kierland and O'Leary's (1941) contraindications to the employment of Swift-Ellis therapy are the following (1) patients who exhibit the clinical signs of neurosyphilis which persist in spite of adequate treatment in whom reactions to tests of the cerebrospinal fluid have become negative (2) patients physically unfit such as those who have advanced tabes dorsalis (3) the presence of the signs and symptoms of advanced involvement and degeneration of the lower part of the spinal cord and (4) cases in which reactions from the treatment are more severe than those resulting from ordinary lumbar puncture

Wassermann fast Spinal Fluid—Goodman and Moore (1935) have studied this important subject and reached the conclusion that the rate and completeness of reversal of the abnormalities of the fluid cannot be used as the sole guide to the duration of treatment Therefore in neurosyphilis as in latent syphilis Wassermann fastness has little significance as a detached phenomenon More recently Forman (1939) while agreeing with this view point felt as the result of experience in a relatively small series of cases that the pushing of chemotherapy either alone or after fever therapy if the latter had been indicated to the point of serologic reversal was worthwhile in the attempt to prevent relapse or progression

Gastric Crisis—The vomiting in syphilitic gastric crisis is central in origin and the administration of cracked ice carbonated waters etc. has usually no effect upon it The physician is therefore quite helpless in the presence of an abjectly miserable patient unless he turns to the sovereign remedies morphine or dilaudid which he often does They control both the pain and the vomiting but not infrequently must be used several times with the result that the patient sometimes has his tabes complicated by morphinism a most difficult combination to treat It is therefore of interest to note that McFarland has reported favorably upon the rectal use of chloral hydrate and sodium bromide in these cases In a series of 49 injections given to 12 patients he obtained in 76 per cent of the administrations fully as great relief as is obtained with opiates He gives a retention enema containing in 15 cc of fluid from 40 to 60 grains (2.6 to 4 Gm) of each drug depending

upon the size of the patient. Unfortunately it would seem that this method is not readily applicable in all cases, since most patients receive several injections of an opiate during their first few attacks while a puzzled physician is trying to rule out gallstone colic, etc.

Marinesco, Sager and Ençon have reported upon the use of 1 to 2 cc. of a 25 per cent sterilized magnesium sulfate solution intraspinally in this condition. In the 8 patients thus treated, pain and vomiting disappeared entirely in from thirty to fifty minutes after the injection. Some patients needed another injection after two or three days, in others the interval was lengthened to several months. Alajovanine and Horowitz (1932) have used successfully intravenous injections of 1 to 3 mg. of atropine sulfate, once or twice daily, for several days. Fellows (1934) has successfully employed forced spinal drainage, consisting of prolonged simultaneous intravenous injection of hypotonic saline solution (3000 to 3500 cc. of 0.45 per cent sodium chloride) and drainage of the spinal canal (withdrawal of 200 to 250 cc. of fluid).

Numerous surgical procedures have been proposed as a last resort, all of them have at least one success to their credit.

Lightning Pains—The only hopeful therapy recently reported (all previously raised hopes having been forlorn) for relief of intractable lightning pains is the use of thiamine hydrochloride (vitamin B₁) intravenously in weekly doses of 10 mg. Metildi (1939) had treated only 6 patients and considered his report distinctly a preliminary one, still, the 6 patients were much benefited, and so the method seems one of promise.

TREATMENT OF CARDIOVASCULAR SYPHILIS

Effect Upon Length of Life—Once aortitis, the earliest of the lesions, has developed the outlook is grave, but Cole and Usilton (1936), as spokesmen for the Cooperative Clinical Group presented authoritative evidence of the following nature: with little or no treatment after detection of the lesion, the average duration of life was thirty-four months, with inadequate treatment it was fifty-six months, with the use of much arsenical and heavy metal, it was eighty-five months. In the cases of sacular aneurysm, the length of life was increased through adequate treatment from thirty-seven to seventy-five months. In cases of aortic regurgitation, the average duration of life in the inadequately treated was forty months after diagnosis, which period was prolonged to fifty-five months when adequate treatment was administered—latterly, Kampmeier and Combs (1940) have analyzed 163 cases at the Vanderhilt University Hospital and decided that treatment does not favorably influence prognosis in aortic insufficiency, it will be very interesting to see how time resolves this difference of opinion.

What Constitutes Adequate Treatment?—In the old days when only mercury and the iodides were available it was felt that relief was sometimes afforded by their use in cardiovascular syphilis and that perhaps in isolated cases life was even prolonged. Then with the introduction of arsphenamine and its use in these cases in full doses without other preparatory treatment, there followed a sad period of many deaths caused in the following three ways: First, ventricular fibrillation, with sudden death during the injection. Second, death within twenty-four to forty-eight hours of an injection by sudden coronary occlusion or rupture of an aneurysm as the result of a Herxheimer reaction. Third, sudden congestive heart failure in

patients not previously showing evidences of decompensation, these deaths being ascribed to the "therapeutic paradox" of Wile, *et al.*, rapid replacement of healing inflammatory tissue in the myocardium, valves and aorta by contracting scar tissue, with the patient left functionally in much poorer condition than before treatment began. So arsphenamine was abandoned and mercury and the iodides fallen back upon again. Nowadays, as the result of cautious retrials with the less drastic neoarsphenamine and mapharsen in small doses, it has been found that if the use of these drugs is carefully preceded by employment of metals and iodides to promote slow resolution of syphilitic inflammatory tissue, the patient is very much better off than when treated without the arsenicals at all. The treatment scheme presented below is that of the Johns Hopkins investigators (see Moore, Danglade and Reisinger in Bibliography) and is fully representative of the type endorsed by the Cooperative Clinical Group.

Treatment of Heart Failure—If there is any evidence of congestive failure when the cardiovascular diagnosis is made, the patient is put at complete rest and is digitalized, though of course the full effectiveness of this drug is rarely experienced in syphilitic heart disease. Unless there is persistent edema no other drugs are given except iodides, if there is edema salyrgan intravenously, or succinimide of mercury intramuscularly, are given for a few days for their diuretic effect. Nitrites, xanthine vasodilators, and sedatives are employed when indicated. Convalescence is made purposely slow and subsequently graduated exercise is rigorously supervised. Ambulant patients are kept on maintenance digitalis dosage, continuously if necessary. Meanwhile when and if a fair degree of cardiac reserve is established anti-syphilitic therapy is begun.

Antisyphilitic Treatment—Continuing the iodides, a start is made with bismuth, using preferably an insoluble suspension in oil because of its slow absorption and beginning with one half doses. These doses are given every four or five days for 4 or 5 injections, and if tolerated, as is ordinarily the case, the full dose is then given once a week. The bismuth and iodide course is then continued ten to twelve weeks before beginning the use of arsenic. If, on completion of the first bismuth course, the patient has not become completely ambulatory without edema or exertional dyspnea, bismarsen is considered the arsenical drug of choice. The intramuscular injections begin at 0.05 to 0.1 Gm. every five days and are increased later to 0.2 Gm. at four to seven-day intervals if no reaction has occurred. Twelve to 20 injections are a course. But if the patient is ambulatory with only slight signs of cardiac embarrassment at the end of the preparatory bismuth and iodide period, neoarsphenamine is used intravenously, nowadays of course many men are preferring mapharsen. The beginning dose of neoarsphenamine is 0.05 to 0.1 Gm., cautiously and gradually increased at weekly intervals to a maximum of 0.3 Gm., which may be only rarely exceeded, mapharsen is likewise reduced in dosage and given with equal caution. The course comprises 10 to 12 injections. Ideally, bismuth and iodide courses are alternated with arsenical courses without intervals for two years, thereafter, if the general physical condition is satisfactory, long rest periods may be instituted, but it is considered probably wise to give a bismuth course followed by one of bismarsen or one of the above arsenicals once yearly as long as the patient lives. The blood Wassermann reaction is usually "fast" and no attention is paid to it.

Whom Not to Treat—Some patients of course never establish sufficient cardiac reserve to permit the use of an arsenical at all, in such the aim should be to alternate courses in which bismuth and iodides are used simultaneously with rest periods of two to four months or with courses of mercury byunction. When it seems inadvisable to treat at all, because of advanced age, extremely poor condition, or the presence in advanced stage of a complicating disease, mercury may usually still be given by mouth with some slight effect, though the danger of adding to misery through induced gastrointestinal disturbance must certainly be carefully weighed. Severe renal impairment precludes the use of both mercury and bismuth, and the arsenicals may not be used without heavy metal preparation. Bismarsen may be cautiously tried. Complicating neurosyphilis may necessitate intraspinal treatment (for optic atrophy), only in instances of very great desperation would a trial of fever therapy be justified. Tryparsamide, however, does not seem to affect the cardiovascular lesion adversely, but when using this drug its current tendency to cause constitutional reactions more frequently than formerly should be borne in mind.

TREATMENT OF SYPHILIS IN PREGNANCY

The authoritative committee, comprising Cole, Jeans, Moore, O'Leary, Parran, Stokes, and Vonderlehr, who prepared a statement on syphilis in pregnancy for the United States Public Health Service in 1940, made a statement which may be condensed as follows: only 17 per cent of the known conceptions in untreated syphilitic women result in living nonsyphilitic children, the remaining 83 per cent terminate in miscarriages, stillbirths, or living children with syphilis, 60 000 of these children with syphilis are born alive each year in the United States. Very obviously in view of this situation the obligation is to discover syphilis if it is present in the mother and then to treat *at the fetus through the mother*. Precisely the steps necessary in attacking this problem were indicated by the findings of the Cooperative Clinical Group a few years ago, in what follows a condensation of their report is interlarded with such recent material as is necessary to bring it completely up to date.

When and Whom to Treat—In the syphilitic woman a negative blood reaction during pregnancy greatly increases the chances for a living apparently nonsyphilitic child, but it is insufficient to insure this happy issue since one tenth of the syphilitic children in the Group studies were born to mothers whose blood was negative during pregnancy. But disregarding the blood reaction it is found that early and adequate treatment in pregnancy will result in 91 per cent of the women being delivered of apparently non-syphilitic babies. The obligation is therefore very clear to examine thoroughly into the possibility of syphilis in the very beginning of pregnancy and to begin treatment as soon as a positive diagnosis is made or history obtained. Infection of the fetus probably rarely if ever occurs before the fifth month so the more time there is for treatment before that period the less likely is the infection to take place. The clinical manifestations of syphilis are often suppressed during pregnancy and therefore routine blood serologic examination is most important. But a negative test early in pregnancy, even if coupled with a negative history, is not sufficient, syphilis may have been acquired after conception took place and therefore ideally, for complete

safety, the test should be repeated at about the fifth and seventh months. McHelvey and Turner (1934) showed conclusively that even if syphilis is discovered late, treatment up to term will still considerably increase the chances of delivering a live, apparently nonsyphilitic child. Gammeltoft found some years ago, and the Clinical Group confirms him, that the syphilitic mother may be delivered of a syphilitic baby many years after the infection, just as a syphilitic no longer capable of transmitting the disease in any other way may give it to another when acting as donor for a blood transfusion. Even a woman completely cured clinically and serologically will occasionally, if untreated, give birth to a syphilitic baby. The safest procedure therefore, considering that it is syphilis in the fetus which we are attempting to prevent, is for every woman who has or ever has had syphilis to take anti-syphilitic treatment throughout each pregnancy regardless of her syphilitic status at the time.

Pregnant Woman's Tolerance of Arsenical Treatment—Despite the fact that it may be fairly assumed that the kidneys and liver of the pregnant woman are already under some strain, the Group found that there is no significant difference in minor arsenical reactions in pregnant and non-pregnant women and that the pregnant woman actually experiences fewer severe reactions. Ingraham (1930) questions this however, for in a statistical study over a five year period in the Philadelphia General Hospital he found reactions to be more frequent in pregnant women, especially gastro-intestinal, renal and hepatic reactions. There are other observers, particularly abroad, who also maintain that susceptibility is heightened. Cole *et al* (1940), in the statement above referred to, have taken the position that only toxic hepatitis and hemorrhagic encephalitis occur more frequently in pregnant than in nonpregnant women or in men. Thus it would seem that the subject of arsenical reactivity is *sub judice*.

Effect of Treatment on the Toxemias of Pregnancy—Ingraham (see above) felt that antisyphilitic therapy may aggravate an existing toxemia or precipitate an incipient one. However, Peckham (1941), at the Johns Hopkins Hospital where vigorous therapy of syphilitic patients has been routine for many years, studied the matter in the records of 13,742 consecutive deliveries and definitely concluded that antisyphilitic therapy does not increase the incidence of the toxemias of pregnancy.

Type of Treatment—If diagnosis is made early, treatment need not vary greatly from that of the charted outline in the discussion of early syphilis on a preceding page, regardless of the stage of syphilis in which the woman herself is thought to be. Cole *et al* (see above) like to alternate 10 arsenicals with 8 bismuths right up to term, adjusting the overlap as may be necessary in order to end on arsenic, if the diagnosis is not made until late in pregnancy. Simultaneous treatment with arsenic and bismuth is advocated. They propose the following rules: (1) 'Always plan to give an arsenical for at least six weeks before delivery.' (2) 'Try to administer at least 20 doses of an arsenical before delivery. If necessary administer mapharsen every five days or if very late in pregnancy twice a week.' The study of Castallo *et al* (1939) of 103 women on mapharsen and bismuth indicated to them that the new drug is not as good as nearsphenamine for this purpose, but I doubt if a larger study, with the adequate controls which this one lacked, would confirm their impression. Ingraham apparently somewhat nonplussed by the

increase in arsenical reactions which he records (see above), raises the question whether more consideration should not be given to adequate preparatory heavy metal therapy before beginning arsenical treatment, this is certainly the opposite of what practically all other syphilologists are advocating and so far as I know has not yet been put to the test

TREATMENT OF CONGENITAL SYPHILIS

Whom to Treat.—Usually the more recent the mother's infection and the less treatment she has had the more likely is the infant to be born with a mucocutaneous, osseous, nephritic, or other severe form of the disease which will take it off despite the most heroic chemotherapeutic and feeding efforts to save its life. But these cases do not pose the big problem in syphilis of the newborn, which is how to determine whether the apparently healthy baby of a treated syphilitic mother is itself syphilitic. Smith (1935) has well reemphasized that there are three periods in which lesions are most prevalent (1) the first six months, when they are chiefly ectodermal, mucocutaneous and osseous, (2) from six to eight years, when they are mostly bony, periosteal and corneal and (3) at puberty, when the corneal and nervous lesions are most likely to preponderate. In the latter two periods keen diagnostic study will often detect the heredosyphilitic even though the signs are not outstanding and much can be done to arrest the progress of the disease through adequate treatment. But it is principally in the first age period, birth to six months, that the best hope of effecting a "cure" lies. A negative Wassermann reaction of the cord blood or of the mother's blood does not rule out the disease in the child. Unfortunately, also, a positive reaction of the cord blood or of the infant's own peripheral blood does not always mean syphilis either, because it has been several times convincingly shown that these early reactions frequently become spontaneously negative and that the infants have not been actually infected. However, Faber and Black (1936) have shown that the quantitative, instead of the usual merely qualitative method of performing the Wassermann test, could be used to considerable advantage, since with it the decline of the test toward zero can be detected by the end of the first week or even sooner, from a limited experience with this test, Ingraham *et al* (1941) are also impressed with its ability to eliminate the nonsyphilitic patient. Roentgenologically, too, much assistance is to be had, for osteochondritis and periostitis, which the experienced man will confuse with no other lesion, appear in almost 100 per cent of cases within the first six months of life. Ingraham (1936) concluded, as the result of considerable study, that osteochondritis usually becomes roentgenologically manifest about five weeks after the fetus is infected, while periostitis requires approximately four months to develop. Serial roentgenographic study throughout all this period in order to detect the first appearance of the lesions is prohibitively expensive but Ingraham was willing to make the prediction that a single roentgenogram made when the infant is six weeks old will detect almost every case, after further study, he (Ingraham *et al*, 1941) seems still of this opinion, adding that most of the conditions to be confused with syphilitic osteochondritis develop at a later period and even then show a type of early change usually demonstrable in congenital syphilis during the first month of life.

The treatment of late congenital syphilis is that of late or latent acquired

syphilis and therefore requires no special consideration here save to say that the disease is often extremely resistant especially when its chief manifestation is interstitial keratitis or some form of neurologic involvement, and, further, that the great rarity of syphilitic aortitis in children and adolescents will lessen to a great extent the practitioner's fear of instituting "therapeutic paradox" (see under treatment of cardiovascular syphilis) in beginning the treatment of these young people. The several special features of treatment in early congenital syphilis are presented below.

Type and Length of Treatment—Since the value of continuous treatment in early syphilis has become fully established, that has become the method of choice in congenital syphilis also. The charted treatment outline in the section on early syphilis will serve as general guide here, but in their authoritative statement for the United States Public Health Service, in 1940 Cole *et al* suggest the following scheme of timing the injections if the infant is not acutely ill.

Week	Treatment.	Week	Treatment.
1	Arsenical in one-third to one-half full dose	29-40	Bismuth—note overlap
2-10	Arsenical in full dose	41-43	Arsenical
10-19	Bismuth—note overlap	43-59	Bismuth—note overlap
20-29	Arsenical	60-63	Arsenical
		65-72	Bismuth—note overlap

If the infant is ill with early congenital syphilis it may do badly under this routine, in such cases it is considered advisable to begin the treatment with heavy metal and just attempt to prevent progression until the patient's general condition has improved. Howard (1939) considers it advisable to attempt some protection of the liver by injecting 50-100 cc of 10 per cent dextrose solution intravenously preliminary to each arsenical injection in the first course.

The accomplishment of negative blood and spinal fluid tests, together with the absence of all signs and symptoms of the disease, are the aims of treatment of course. Smith, at Johns Hopkins Hospital, permits probation if these criteria are satisfied after one year's treatment, but in blood Wassermann fast cases he does not allow a rest period until the spinal fluid is found normal and treatment has continued through an arbitrary two years—persistence in these Wassermann fast cases being due to his observation that relapse or progression is four times more frequent among them than among those in whom Wassermann reversal is secured.

Neocarsphenamine and Bismuth—For this classical form of therapy Stokes and Ingraham (1939) advise the following dosage weekly, to be used in some such scheme as that in the table above.

Neocarsphenamine 10-15 mg/kg (5-7.5 mg/lb)

Bismuth 2-4 mg/kg (1-2 mg/lb)

(The bismuth content of commercial preparations is stated on the package.)

In infants and young children jugular vein injection is easy of accomplishment lay the child on the table with the head dependent and turned to one

side, crying brings out the jugular vein very promptly. Injection may also be made under the fascia of the scalp. Injection into the fontanel is very dangerous. The bismuth is given intramuscularly of course.

Mapharsen—The reports of Morgan (1933), Astrachan (1938) and Howles (1939) all indicate that the drug bids fair to replace neoarsphenamine in the treatment of congenital syphilis since it is apparently fully as effective and certainly causes fewer reactions. Cole *et al* (1940), previously referred to state the appropriate dosage to be 0.5–1.0 mg per kilogram (which is about 0.25–0.5 mg per pound).

Bismarsen—This drug has the definite advantages of being given intramuscularly and of containing both arsenic and bismuth. Chambers and Koetter used it in 180 patients ranging in age from birth to fourteen years, the majority being more than three years old. Reilly's series comprised 170 children in about the same age range. It appears that active lesions heal somewhat more slowly than under the straight arsenicals (Reilly [1935] demurs, however) though the ultimate result is quite as good. All observers are agreed that improvement lags in interstitial keratitis.

Stokes and Ingraham (1939) state the dosage as 7 mg per kilogram (3.5 mg per pound). Injections are given once or twice weekly in courses of twenty with rest intervals of two weeks between courses. Bismarsen reactions in the adult are discussed on a preceding page, in children they perhaps occur less frequently and are less severe.

Sulfarsphenamine—This drug has the following advantages when substituted for neoarsphenamine or mapharsen in the arsenical bismuth regime: (a) Though given intramuscularly, it is fully as effective as the intravenously administered drugs, (b) It is easy to prepare by merely dissolving it in the ampule in 1 to 2 cc (the less the better) of fresh, sterile distilled water, (c) The solution is much more stable than that of neoarsphenamine, though of course mapharsen is also stable in solution, and (d) The discomfort due to injection is slight and the immediate reactions few. There is however, one outstanding objection to the drug: it is the most toxic of all the arsphenamines when given to adults, and though these serious reactions do not seem to occur with nearly so great frequency in infants and young children, the danger must always be held in mind. Stokes and Ingraham (1939) state the dosage as 10 mg per kilogram (5 mg per pound).

Acetarson (Stovarsol)—This arsenical compound has been much used in the treatment of congenital syphilis on the Continent for a number of years but Whipple and Dunham (1933) who have exhaustively and authoritatively reviewed this literature state that of about 40 reports only 4 could be found in which sufficient follow up had been made to evaluate the drug. The most recent favorable American reports are those of Traisman (1935), Lyon *et al* (1939), and Goltman (1940), an important unfavorable report is that of Pillsbury and Perlman (1930). The advantage that acetarson can claim to have over the other arsenicals is that it can be given by mouth—but that is the sole advantage. It is cheaper than the other drugs, to be sure, but that will be a point in its favor only when it shall have been shown to be fully as satisfactory in completely "curing" congenital syphilis. The fact that acetarson can be given into the hand of a child who visits the clinic or office alone and who is then told to take it home and insist that his mother administer the doses to him faithfully, can only be considered an advantage by

wishful thinkers Furthermore, I cannot for the life of me understand why bismuth shall cease to be given once the use of this drug has begun Is it that, having spared the child the arsenical half of his injections, we are under some sort of obligation to omit the bismuth portion too? Not all the Continental workers discarded in the beginning, nor have they yet discarded, the use of heavy metals between acetarsone courses

The principal findings with regard to the drug by Pillsbury and Perlman, who studied its use in 187 patients at a children's clinic of the University of Pennsylvania Medical School, were the following (a) It is an active anti-syphilitic agent but its action is less rapid and less satisfactory than that of arsphenamine and bismuth preparations, (b) The incidence of all reactions and the proportion of serious reactions, was very high, (c) Nephritic reactions occurring suddenly and insidiously are the greatest single drawback to the use of the drug, (d) Acetarsone is probably not administered as directed at home for the incidence of reactions among patients under controlled conditions in the hospital was four times that of the out patients Acetarsone is not Council accepted for the treatment of syphilis

The high dosage latterly employed has already been revised and nearly all users of the drug have gone back to the scheme of Bratusch Marram (1931), which follows

One week	0.005 Gm per Kg daily ($\frac{1}{4}$ grs n per 2.2 lbs.)
One week	0.010 " ($\frac{1}{2}$ " " ")
One week	0.015 " ($\frac{3}{4}$ " " ")
Six weeks	0.020 " (1 " " ")

Length of course nine weeks Rest period between courses, six weeks

Acetarsone is commercially available in tablets of several sizes Yam-polsky (1934) orders all tablets to be made into powders the patient then receives 21 powders weekly and is instructed to take 1 powder dissolved in water three times daily, one half hour before eating, or the dose is given infants in the same way before feeding time

Resistance of Interstitial Keratitis and Neurosyphilis —Under all systems of treatment amelioration of interstitial keratitis usually lags woefully behind improvement in other respects Still, Cole *et al* (1937), reporting for the Co-operative Clinical Group, found that of patients treated with arsenicals and heavy metals within six months of the onset in the first eye, the involvement remained unilateral in 71 per cent, and that of all the patients with acute involvement six times as many untreated as treated individuals lost useful vision In the Group's most recent report, Klmder and Van Doren (1941) advise that fever therapy be employed as soon as possible after the onset Iodides are not to be used as they unfavorably influence final visual acuity, but the arsenicals and bismuth are to be administered according to the following schedule

Weeks	Weeks
1 to 9 Neocarsphenamine 10 weekly doses	40 to 44 Neocarsphenamine 5 weekly doses
Bismuth (soluble) 8 doses, twice weekly during first month	45 to 49 Bismuth, 10 weekly doses
10 to 19 Bismuth 10 weekly doses	50 to 59 Neocarsphenamine 5 weekly doses
20 to 29 Neocarsphenamine 20 weekly doses	60 to 69 Bismuth 10 weekly doses
30 to 39 Bismuth, 10 weekly doses	70 to 73 Rest period
	74 to 83 Bismuth, 10 weekly doses

The most interesting new development in the treatment of this entity is Sydenstricker's (1941) report of the successful employment of riboflavin (see Index for methods) in several cases. An ophthalmologist should see the case also for the proper use of atropine and diosine locally may greatly contribute toward cure.

The treatment of neurosyphilis in congenital syphilitics is the same as in syphilitics having the acquired form of the disease but it is rarely successful. Indeed, progression often takes place in spite of the most vigorous use of drugs. O'Leary and Welsh (1933), and Wile and Hand (1935) report almost complete failure with fever methods also.

TREATMENT OF LATE (TERTIARY) SYPHILIS

The typical forms of late syphilis of the liver—diffuse hepatitis, syphilitic cirrhosis, and hepatic gumma—call for utmost caution in the therapeutic attack. A Herxheimer reaction in this organ may be fatal or the patient may die in what Wile so well calls the 'therapeutic paradox.' This latter is a state of affairs characterized by such rapid healing and cicatrization that the portal circulation is obstructed, with resultant ascites, or the bile ducts are occluded to such extent that the most severe jaundice develops. Treatment should therefore have as its aim the very leisurely promotion of reparative processes. Authorities are agreed that except in the rarest of instances the arsenicals and bismuth are absolutely contraindicated. Therapy should consist in continuous moderate to heavy use of the iodides with mercury courses superimposed upon this, about as follows: iodides one week, iodides and mercury by mouth, two weeks, iodides and mercury injections eight or nine weeks (occasionally giving a little mercury by intramuscular injection instead of the rubs if this seems desirable), iodides alone for about four months, then go through the cycle with mercury again and repeat this several times as dictated by progress in the case. If iodides are omitted for a while it had better be during one of the periods when mercury is being given. The vast majority of patients are very much improved by such treatment as this.

In practically none of the other usual types of late syphilis—gastric and the rarer intestinal and rectal forms of gastro-intestinal syphilis, cutaneous and mucosal manifestations of diverse nature, osseous and joint syphilis, etc.—need Herxheimer reaction or the 'therapeutic paradox' be feared. Treatment can therefore begin with the use of arsenic and can in general proceed much as in the treatment of acute syphilis. However, since most of these patients are in or approaching the years in which cardiovascular, neuro- and hepatic syphilis (all absolutely contraindicating sharp attack) may be expected to occur, every diagnostic aid should be utilized to make sure that one or more of these entities is not present as a complication. Some men favor beginning the treatment always with bismuth in these cases even though the patient seems to be clear of all syphilitic involvements save those relatively harmless ones which are presenting; progress is thus much slower of course. In some instances 'mixed treatment' with mercury and iodides (see above) will alone be indicated; judgment must be exercised in each individual case. In the presence of a severe complicating nephritis only the iodides can be used with full safety. In late syphilis of the bones and joints

surgical and orthopedic aid may be highly desirable; indeed in Charcot joints accompanying tabes, the antisyphilitic attack is of itself impotent.

IODIDES IN THE TREATMENT OF SYPHILIS

In numerous places throughout the discussion of syphilis I have referred to the use of iodides and wish here to set down briefly the more acceptable forms of iodide therapy.

Potassium Iodide.—By Mouth.—This is the cheaper salt and the one most frequently used. It is often stated that the sodium salt should be given the preference because of the depressing effect of the potassium ion on the heart, but Eggleston pointed out some years ago that potassium is eliminated from the human body with such rapidity that it is almost impossible to poison the heart by the administration of its salts by mouth; nevertheless, Steward and Smith (1941) have demonstrated some very interesting electrocardiographic changes in patients taking potassium iodide, and one wonders whether the subject might profitably be reopened. Osborne's investigations at the Mayo Clinic suggest that the iodine given in the form of potassium iodide by mouth forms a sodium protein combination, while in the case of sodium iodide by mouth only traces of iodine enter into combination with the proteins—observations which may bear directly on the general clinical impression that, grain for grain, potassium iodide is more effective than sodium iodide.

As to dosage, I quote Barker and Sprunt: "Potassium iodide is usually prescribed in strong solution, an ounce of the salt being dissolved in an ounce of water, with the direction that the drug shall be greatly diluted as each dose is administered. Since an idiosyncrasy to the drug may be encountered, small doses are usually given at first, say 5 grains [*i. e.*, 5 drops of the solution—H.B.], three times a day, preferably given a half or three quarters of an hour after meals. Even when mild symptoms of iodism occur, they will usually disappear on increase of the dosage to 10 or 15 grains thrice daily. The dose has sometimes been increased, up to 300 grains (20 Gm.) or more a day. Large doses may cause gastric irritation, due to the salt action, symptoms that are quite distinct from those of iodism. This irritation may be obviated to some extent by administering the drug in milk or whey. Engman warns against the use of the excessive doses sometimes employed, especially in certain health resorts where many patients are treated. Fournier was also strongly opposed to what he called 'iodide debauches'; he seldom gave more than from 45 to 60 grains daily. When tolerance for the drug is established, the curative value apparently diminishes and the dose must therefore be increased."

The following prescription is probably as effective as any in disguising the drug; it will contain 15 grains (1 Gm.) in the teaspoonful dose:

R Potassium iodide.	3j	30 0
Compound syrup of sarsaparilla	3j	30 0
Water to make	3iv	120 0

Label: One or more teaspoonfuls in water as directed

Sodium Iodide Intravenously.—Stokes feels that Osborne's work on the comparative penetrability of the nervous system by iodides when administered by mouth and by vein warrants the giving of sodium iodide intra-

veously 10 selected cases of neurosyphilis. He gives 30 to 150 grains (2-10 Gm) in this way three to five times weekly, full doses by mouth being given meanwhile.

Iodism—The symptoms are those of a "common cold" plus any one of a number of types of skin rashes, the latter often appearing some time after the former and occasionally, as in the astonishing case reported by Montgomery (1940), assuming a bizarre form. Some individuals never manifest these symptoms even on enormous doses, while others do so regularly when a certain dosage is reached. It is usually possible to disregard the iodism but in some cases the drug must be omitted or greatly reduced for a time. Fever sometimes accompanies the other symptoms but fever as the sole manifestation of iodism, as reported in 2 cases by Katzenstein (1938), must be a rare occurrence. The possibility of an iodide cachexia in persons who have been taking the drug regularly for a very long time, must always be borne in mind. I think many of these cases pass unrecognized in some clinics.

Organic "Iodides"—More or less complex iodine compounds with proteins and fats and one with methecoamine (urotropin), have been introduced with claims that they are less irritating to the digestive tract than the metallic iodides and that they are less inclined to cause iodism. When given in the doses advised by the manufacturers they are usually distinctly less irritating to the stomach, but it is not quite certainly known whether these nonirritating doses are therapeutically as effective as the doses of metallic iodides that do cause irritation. Regarding the occurrence of iodism, it is doubtful if a susceptible individual will escape this symptom-complex if these newer preparations are used in doses comparable to those employed in the treatment with the older simple iodides. The following are the principal preparations: iodalin, supplied in 5 grain (0.3 Gm) capsules, iodo-casein, 5 grain tablets, iodostarine, 4 grain (0.25 Gm) tablets, lipiodine, 5 grain tablets, iodine, 3 grain (0.2 Gm) capsules, calcium iodobenzenate (sajodio), 1- and 5 grain (0.06 and 0.5 Gm) tablets, siomoe, $\frac{1}{2}$, 1, 2- and 5 grain (0.03, 0.06, 0.12, 0.3 Gm) capsules.

PROPHYLAXIS OF SYPHILIS

See under "Prophylaxis of Venereal Diseases"

TETANUS

(Lockjaw)

"Another received an insignificant wound to speak of (for it was not deep) a little below his neck behind from a sharp dart which being taken out not long after he was drawn and distorted backwards as in the opisthotonus. His jaws were also fastened and, if anything most was put into his mouth and he attempted to swallow it it returned again thro' the nose. In other respects he grew worse immediately. The second day he died."

—Hippocrates. Upon Epidemics. Book V. The Cases at Salamis—No. 15.
(Translated by Clifton, London, 1734)

Tetanus is an acute infectious disease caused by the infection of a wound with the spores of *Clostridium tetani*. The wound is usually an accidental

oae, though the organism has also contaminated burns and bedsores and suppurative otitis media. Tetanus neonatorum is becoming very rare now that the umbilical cord is properly cared for as a matter of routine, and tetanus following an abdominal operation is also nowadays a rare occurrence. Wainwright's (1926) compilation of 760 cases showed that 80 per cent were due to injuries on the street, on the farm, in homes, gardens, stables, etc., and only 20 per cent to industrial accidents. That even our modernly constructed smooth surface streets are still a potential source of danger has been shown by the timely studies of Gilles (1937). Bush (1941) reports an interesting group of 5 cases (4 deaths) attributable to the introduction of a graze pad into the cervix by an abortionist. The fact is now well established that the organism is harbored to a very considerable extent in the human intestinal tract as well as in that of the lower animals. Bauer and Meyer found spores of definitely toxic strains in 24.6 per cent of 487 specimens of feces from residents of California.

The interesting studies of Lahiri (1939), in India, indicate that there is no such thing as an environmentally acquired immunity to tetanus, i.e., farmers and others exceptionally exposed do not apparently acquire specific antitoxic protection through subclinical infections. The tetanus organism grows best under the completely anaerobic conditions prevailing in deep wounds or those that have become scabbed over, and its growth is also aided by the concomitant presence of pus producing organisms, the retention of a foreign body in a fresh wound also increases the chances of tetanus developing. However, tetanus occurs frequently from wounds so trivial that no attention is paid to them.

Until very recently the almost universal belief has been that the toxin produced by the bacillus at the wound site reaches the central nervous system by traveling along the axis-cylinders of nerves or by way of the perineural lymphatics. Now, however, studies initiated by Abel in 1934, and currently being pursued by his associates, particularly Piror, indicate that the only way the toxin can reach the central nervous system is by the blood vascular pathway; these workers are now even suggesting that the tetanus toxin in the cord is altered into or liberates a different agent which is transported to and has its lethal effect upon the vital centers. Of such disturbing heresies is our present great epoch compounded!

The prodromal symptoms which it is important to recognize, are restlessness and hyperirritability, perhaps chilliness and headache with some general stiffness of the body, and, the most important symptom a stiffness of the neck and difficulty in chewing and swallowing. A boardlike rigidity of the abdomen makes its appearance very early. The later, more typical, symptoms are frequent convulsions from which the patient does not at any time completely relax, the characteristic lockjaw (trismus), a sardonic facial expression, several degrees of fever with proportional leukocytosis, spinal fluid that is clear but under increased pressure, and great pain from the severe muscular contractions, consciousness is often retained until the end death usually occurring on the fourth or fifth day. It is said that if a patient survives the eighth day his chances of recovery are very good.

The incubation period of the disease is from three days to several weeks. Statistics, gathered from civil as well as military practice, show that most cases develop within from ten to fourteen days after the wound is suffered,

it is axiomatic that the shorter the incubation period the higher the mortality. Since the prophylactic use of tetanus antitoxin has become more frequent, a local type of the disease with symptoms confined to the neighborhood of the wound, is rather often seen. The mistaken tendency is to recognize this as a new entity, though there are records of numerous such cases before the introduction of antitoxin, sometimes these local tetanic foci precede by some time the signs of descending tetanus.

Mortality in tetanus is as high as 40, sometimes even 70 to 80 per cent. A few recent reports are showing an appreciably lower mortality than this under modern therapy, but it seems unwarranted to eliminate those who die within twenty-four hours of admission, as some authors are doing in order to obtain the low figures, indeed, Dietrich (1940) feels that probably many of these early deaths are due to faulty therapy since they occur much sooner than they possibly could have done in untreated tetanus.

Vener and Bower (1940) report a second attack of tetanus in the same patient and mention five other cases in the literature.

THERAPY

Sedatives—Certainly the judicious employment of all available sedative measures is indicated in tetanus for it is our bounden duty to lessen as much as possible the terrific suffering of these patients. Spaeth (1940), in a recent careful analysis of results over a period of years in his hospital, believes that even from the standpoint of reduction in mortality one is justified in placing great emphasis upon effective sedative therapy. He prefers avertin solution in the form of a retention enema, using 25 mg per kilogram (12.5 mg per pound) of body weight for the initial average dose to be followed at fifteen to thirty minute intervals with about half that dosage according to individual requirements. Sometimes initial dosage may have to be double that stated if the patient is having severe asphyxial spasms. No deleterious effects of avertin, other than slight transient rectal irritation, have been reported by any of the numerous observers, but Spaeth would prefer not to use it if there are renal or hepatic disorders. In one very severe case of tetanus neonatorum in an infant eight days old, Cole and Spooner (1935) used avertin in full adult dosage per pound of body weight and believed that this heroic measure saved the child's life, for twenty-five consecutive days the patient received never less than two instillations daily and for the first thirteen days often as many as four, five or six.

Sodium amytal may be given by mouth, rectum, vein, or by intramuscular injection. Spaeth's routine initial dosage is 5 mg per kilogram (2.5 mg per pound) of body weight, with an upper limit of 240 mg for children and 480 mg for adults. One cannot too strongly stress that any barbiturate given intravenously must be given *exceedingly slowly*, my own feeling is that these drugs had best be given intramuscularly. Dietrich was well pleased with *secenal* in the 3 cases in which he tried it, using "knock-out doses" of 3 to 4 grains (0.2 to 0.25 Gm) every three to four hours in a child of five years. Phenobarbital sodium (luminal sodium) is also used, 3 to 6 grains (0.2 to 0.4 Gm) is average adult dosage. Chloral hydrate is well absorbed from the rectum, 30 to 45 grains (2 to 3 Gm) in olive oil or water every four hours is permissible dosage. Paraldehyde may also be given rectally 1 to 6 drachms (4 to 24 cc) in a few ounces of physiologic saline solution. This

last drug was used in the majority of Yodanis's (1937) series of 438 cases, in India, 4 drachms (16 cc) in 2 ounces (60 cc) of physiologic saline solution by the drop method four hourly, varied according to individual requirements. Morphine is valuable but must sometimes be given in doses so large as to be dangerous. As a matter of fact Firor's (1940) investigations indicate that the lethal agent in tetanus (the secondarily formed agent previously referred to) may act chiefly on the respiratory center, if this is proved to be a fact of course caution in the use of these respiratory depressant drugs would be doubly enjoined, and this would apply also of course to magnesium sulfate (see below).

First used by Blake in a case of human tetanus in 1906, magnesium sulfate has off and on had its advocates but does not seem to have made a sure place for itself. If complete relaxation is sought with the drug it may be very dangerous, but used in moderate dosage it should not be. Calcium chloride will very specifically and immediately combat excessive respiratory depression caused by magnesium sulfate, inject 10 to 20 cc of a 2.5 per cent solution of calcium chloride in physiologic saline intravenously (slowly). The following is a summary of the magnesium sulfate dosage which serves Smith and Leighton as a working basis. *Subcutaneous* 1 to 2 cc of a 25 per cent solution for each 20 pounds of body weight, four times in twenty-four hours. Should be continued until disappearance of symptoms. *Intramuscular* lightly anesthetize with ether and deposit intramuscularly 2 cc of a 25 per cent solution for each 20 pounds of body weight, effect in less than half an hour and lasts two or three hours. *Intravenous* most prompt but fleeting effect may disappear in thirty minutes. Dose 6 per cent solution, at rate of 2 to 3 cc per minute until relaxation begins. *Intraspinal* effect in less than half an hour and relief lasts twelve to thirty hours. Anesthetize with ether and inject 1 cc of a 25 per cent solution for each 20 pounds, second dose, 0.8 cc for each 20 pounds, only 0.5 cc per 20 pounds in a child. The most recent report is that of Arnold and McDaniel (1939), who have employed all the above methods of administering magnesium sulfate except the intravenous, the latter being omitted because they thought it too dangerous and because injection by the other routes was very efficacious.

Antitetanic Serum—There has been much skepticism in the profession regarding the value of antiserum in treatment, but recent writers seem to be favoring it again. Statistically, it has certainly not been possible to attest its worth for the reason that there are several variable factors: the severity of the case, the length of the antecedent incubation period, the general condition of the patient (i.e., his ability to withstand attack of any sort), the amount of prophylactic serum that was used, and the coincident employment of other therapeutic measures. Likewise, and for similar reasons, the matter of the preferred route of administration of the serum remains a controversial one. I shall summarize here the antitoxin method employed by Vener and Bower (1941), of Los Angeles, because it is based upon sufficient experience to give it significance, and being a very recent report is an expression of current practice. After a preliminary injection of antitoxin around the wound site (see Local Treatment, below) they inject 60,000 units of antitoxin intramuscularly. Then, as soon as sedation makes it possible, the occipital area is shaved and cisternal puncture is done, removing 10 cc of fluid and slowly injecting by the gravity method 20,000 units of antitoxin. When

the rise in temperature induced by the cisternal therapy has receded to about 102° F (39° C) rectal, 40 000 units of antitoxin are given intravenously, it is diluted in 300 to 500 cc of saline and given by gravity, allowing at least an hour for completion of the injection. If there has been no systemic reaction to this first intravenous injection in four hours, a second of only 20,000 units but in the same amount of saline is given. Twelve hours after the second intravenous injection an intramuscular injection of 40 000 units is given, if reaction caused the omission of the second intravenous injection, this intramuscular injection is increased to 60,000 units. About 200 000 units have now been given within thirty to thirty six hours, thereafter additional large doses are not given unless the patient relapses, but 1500 units are given subcutaneously at four- to five-day intervals for four doses to 'keep the patient desensitized,' and if future orthopedic or other surgical measures are to be taken these doses are continued until two weeks after this intervention.

Space would not permit citing the arguments of all those who disapprove the above type of therapy, but Spaeth (1940) probably summarizes the position in stating his feeling that intraspinal and intracisternal therapy are to be avoided because of the excitement caused the patient, the technical difficulties in the presence of highly spastic states, and the danger of inducing sterile or septic meningitis in subjects already dangerously hyperexcitable. On the basis of titration studies performed by himself and by others earlier, Spaeth does not see the rationale of large and repeated dosage of serum. He proposes a single dose of 40 000 to 60,000 units to be given intramuscularly or intravenously, the larger dose and the intravenous route for those admitted during the first four or five days of the disease. Dietrich (1940) says that in children at least, both the intrathecal and intravenous routes are very dangerous and he prefers to run the risk of a slower effect by giving the drug intramuscularly, he likes to supply a continuous but moderate amount of antitoxin to neutralize any new toxin liberated and believes the administration of 10,000 to 20,000 units daily for two to four days is adequate for this purpose.

Reactions—Vener and Bower say that if a patient is especially sensitive to horse serum or subject to some type of allergic attack, or previously has received prophylactic antitoxin followed by a serum reaction, the intravenous and intrathecal procedures should be omitted and instead two intramuscular injections of 100,000 units each should be given with an interval of twelve to eighteen hours. Spaeth routinely injects adrenalin (epinephrine) and atropine before injecting serum, even intramuscularly, in all patients whether known to be sensitive or not, the serum injection to be made not earlier than thirty minutes after this preparatory injection. His dosage follows:

	6 mo	2 years	5 years	Adult
Adrenalin (1:1000)	3 minims (0.18 cc.)	4 minims (0.25 cc.)	5 minims (0.31 cc.)	8 minims (0.49 cc.)
Atropine sulfate	1/200 grain (0.12 mg.)	1/250 grain (0.24 mg.)	1/200 grain (0.5 mg.)	1/100 grain (0.8 mg.)

Serum sickness (see Index) is usually reported to occur in eight to ten days in half or more of those receiving the antitoxin, in Vener and Bower's series of 100 cases there was an incidence of only 39 per cent, which they at

tribute to the refinements in serum manufacture in recent times. A bovine serum has been available for some years but does not seem to be much employed. In a markedly sensitive individual, Schaeffer and Myers (1941) have successfully employed a horse antitoxin "despeciated" by a method devised by Coghill *et al*. Any type of tetanus antitoxin must be warmed to body temperature before injection.

Toxic neuritis of various nerves, including the auditory, has been reported a few times after the use of tetanus antitoxin.

Local Treatment—Miller lays down the principles of local treatment as follows: "1 Sterilization of the part 2 Thorough opening of the wound in its whole breadth and depth 3 Debridement—complete excision of every scrap of dead or infected tissue 4 Sterilization of the wound 5 Measures to keep it open. It must not be packed, though gauze preferably soaked in hydrogen peroxide, may be laid gently in it. It must not be tightly bandaged. Anything tending to close the wound, and shut out the air, must be avoided. The dressing should be renewed very frequently."

In writing of the sterilization of the wound, one should perhaps specifically mention the tincture of iodine, for it not only tends to prevent secondary infection but seems to have a local specific effect against the toxin. MacConkey and Silva have shown that mixing iodine with toxin definitely lessens the strength of the toxin. There are no data known to me to show whether or not this property is common to all the penetrating disinfectants, such, for instance, as the dyes which have become so popular for local use.

In regard to the matter of thorough incision and excision of the wound it is of interest to note that Sir David Bruce has stated that surgeons were slow to realize the importance of this method during the first World War, but that, had the war lasted longer, tetanus would probably have been extinguished. More recent writers urge not only debridement of the open wound but that all apparently healed wounds be opened widely and foreign bodies sought and removed. It is also considered advisable to give the first dose of antitoxin, as soon as the patient is anesthetized and before beginning any surgical manipulations which may spread the toxin. Vener and Bower (1941) precede surgical procedures forty-five to sixty minutes by injecting 20,000 units of antitoxin completely around the lesion and then keep the operations within this encircled field. Subsequently they treat the area as though infected, using hot compresses of potassium permanganate solution.

Spaeth (1940) is in disagreement with the above position, feeling that under no circumstances should one resort to amputation, excision or drainage for the sole purpose of removing foci at which toxin is being elaborated—at least he stresses that sedation and antitoxin are of primary importance and that thereafter the handling of the local lesion should simply be in accordance with the principles of surgery in the absence of tetanus. Unfortunately, in children and in adults who environmentally sustain trivial wounds with great frequency the inciting wound is often not identifiable and thus local measures cannot be applied even though they might have been desirable.

All surgeons are in agreement that the wound should under no circumstances be cauterized, for the resulting area of necrosis is altogether to the taste of the tetanus organism.

Miscellaneous Drugs—*Curare*, the South American arrow poison which paralyzes voluntary muscular movement by blocking the passage of impulses

from the motor nerves to muscles, has been introduced into medicine and abandoned again on several occasions. The latest reports I have seen were those of Cole (1934), Mitchell (1935), and West (1936), who either employed the crude drug or its chief active principal, curarine. There is no very good evidence, however, that anything of much practical value has come out of these studies as yet. *Phenol intraspinally* was knocking about for a good many years before Swansa reported some apparently good results with it in a small series of cases, in 1931. Since then Thompson and Friedman (1941) have failed to find any rationale for the employment of this agent in their careful experimental studies, and since the proportion of serious reactions was high in Swansa's cases I feel that description of the methods of employment may be well omitted from this edition of the book. There came out of France, in 1938 a report of the successful employment of *alcohol intrataneously* (10 to 40 cc daily of a 33 per cent solution in 30 per cent dextrose), but I have heard nothing further of this. Vener and Bower (1941) are giving *methenamine (urotropin) intrataneously* in doses of 15 grains (1 Gm) with a list of four rationalizing reasons, none of them impressive, it is doubtful if many others will follow this practice.

General Nursing and Dietary Care—Upon the whole the advantage of keeping the room darkened and as quiet as possible has not been stressed in the literature as much as it might have been, reflex spasms can be considerably reduced in number by these measures alone. It seems hardly necessary to mention that someone in attendance should watch the patient unobtrusively at all times so that artificial respiration may be quickly applied as soon as needed. A liquid diet (see Index) is preferred because of the greater ease with which it may be swallowed, but in some instances when sedative measures have not sufficiently relaxed the jaw to permit the administration of food by mouth, nasal duodenal tube feeding (see Index) will have to be resorted to. Rectal feeding (see Index) is less satisfactory for the reason that the patient in tetanus needs more food than can usually be given by that route, furthermore, sedatives are likely being given rectally. The advantages of intravenous dextrose administration should not be overlooked. Constipation is often present and requires the use of enemas in preference to cathartics. Bladder distention should be relieved by catheterization before it increases the patient's restlessness. There is no contraindication to warm sponge bathing unless it aggravates the spasmodic condition.

Pneumonia is the great enemy to be forestalled if possible by keeping the patient off his back and shifting him from side to side frequently, also by attempting to maintain oral hygiene through gentle cleansing of mouth and nasal passages and at times the use of a suction apparatus to take up the secretions which cannot be easily swallowed. Vener and Bower (1941) advocate shrinking the nasal mucous membranes at frequent intervals in the attempt to avoid sinusitis. Moderate elevation of the foot of the bed may also be helpful.

PROPHYLAXIS

This subject has nowadays to be considered under several separate heads: passive immunization with antitoxin at the time of injury, active immunization with toxoid before the receipt of injury, and the combination of the two methods.

Passive Immunization with Antitoxin—The injection of antitoxin at the time of receipt of a wound thought likely to eventuate in tetanus is not an infallibly protective measure but its great efficacy is now so universally recognized that I shall not labor to prove the point here. The objectionable features of this type of prophylaxis, however, are several (a) The protection conferred lasts only for ten to fourteen days, and hence if the wound has not healed in that time or is a lacerated one containing dead spaces, a foreign body or necrotic tissue, the dose has to be repeated at intervals of a week to ten days (b) Subsequent injuries, or reactivation of a latent infection, require further antitoxin injections (c) The reactions characteristic of its therapeutic use are also to be expected when it is used prophylactically, of Newell and McVea's (1940) 500 patients, 59 experienced a reaction of some sort, the reaction being a general systemic one in 22 instances (d) For best results the serum should be kept in a refrigerator

The dosage employed is almost universally 1500 units, given intramuscularly, but this is well increased to 5000 units if the injury is of the suspicious nature above described. Spaeth (1940) says that in the event one or more days have elapsed after the receipt of such a wound, the minimum initial dose should be 20,000 units

Active Immunization with Toxoid—Since the toxoid method was introduced by Ramon and his associates a great deal of work has been performed all over the world to determine the best way of using this agent. The present thoroughly established facts may be condensed as follows from the recent excellent review of Jordan and Halperin (1941) (a) The value of this type of immunization has been established by laboratory determinations of the levels of antitoxin in men and animals and by clinical experiences such as that obtained during the evacuation of Dunkirk, when not a single case of tetanus occurred in those so protected though many of them arrived in Britain five or six days after being wounded (b) Such immunization should be employed by all military personnel, by farmers and certain industrial workers, and by all others whose occupations or avocations make them especially liable to tetanus infections (c) The toxoid should be administered routinely to all children (d) How many millions of persons—and animals, for tetanus has always taken a high toll among horses—have been injected with toxoid is not accurately known, but the number is enormous and reactions which are nearly always mild, are exceedingly rare (e) Wide application of this type of immunization is expected ultimately to effect practical elimination of tetanus as a disease of major importance

The method of immunization practically universally employed in civilian practice is to inject 1 cc of alum precipitated tetanus toxoid subcutaneously in the deltoid region and repeat after three months. The value of a third 'boosting' dose after a similar or longer interval has been shown by numerous investigators, but practice seems now to have settled down to one or the other of the following (a) in children routinely immunized by the two basic doses give another dose every two years, (b) give another dose to anyone receiving a suspicious type of injury

One of the great advantages of alum precipitated toxoid is the fact that it does not deteriorate in the field away from refrigeration. This seems to be the preparation used in our Navy (Hall, 1940), but in the Army (Surgeon General's Circular Letter No 34 June 28, 1941) plain toxoid is being used

(for reasons not known to me) in 3 doses of 1 cc each at three- to four week intervals, subsequently another dose will be given at the end of one year, upon departure for a theater of operations, upon being wounded or burned or operated in such way as to manipulate an old wound

Gold (1940) has proposed an interesting variant in the matter of maintaining immunity through the use of "boosting" doses. He drops a specially prepared preparation ('tetanus toxoid topigen') intranasally, 0.1 cc into each nostril on three successive days, and proposes that these instillations be repeated every six months. If Gold's findings are confirmed as they are likely to be for his preceding work has been of importance in this field, this method would seem to be a particularly suitable one for use in children.

The statement is generally made that toxoid may be given to allergic individuals with no more apprehension than in the case of the nonallergic, but is perhaps not strictly true for a few cases of general reactions have been recorded which seemed to be related to the allergic constitution of the patient. Cooke *et al* (1940) warn that preliminary skin testing with the toxoid should always precede the administration of the second dose, but as these authors are specialists in allergy I think one may perhaps consider them a bit unduly alarmed, however, their admonition to watch the patient for half an hour after the injection and to have a syringeful of epinephrine (adrenalin) solution handy, is certainly acceptable to all.

Diphtheria-tetanus Toxoid Combined—Many pediatricians are routinely immunizing infants and children with the combined toxoids which have been amply shown each to exert their antigenic properties uninfluenced by the other. Digler and Werner (1941) have recently thoroughly studied the subject and find that this practice has everything in its favor and apparently nothing against it. They prefer 2 injections at an interval of three months or more (for a comprehensive immunization schedule see Smallpox). They find it apparently safe to administer these toxoids to allergic children.

Active-passive Immunization—When an individual not previously immunized, receives a protective dose of tetanus antitoxin at the time of an injury, the question often arises whether this is not also a good time to begin toxoid injections, in short, may not the total immunity be greater if one engrafts an active immunity, through toxoid injections, upon the passive immunity obtained by use of the antitoxin? Ramon (1940), who certainly should be listened to, answers in the affirmative, but there are numerous evidences, notably in the work of Frey and Schmid (1939), and Otten and Hennemann (1939), that experimenters in this field are not satisfied with this answer. As things stand, I should say that one should not undertake such a procedure.

TONSILLITIS

Acute tonsillitis is characterized by a rather sudden onset with aching pains throughout the body, very sore throat, high fever and rapid pulse, and considerable prostration. Susceptible individuals often have an annual attack some time during the inclement months, the usual duration is three

to eight days. The possibility of diphtheria is usually easily ruled out by a careful examination of the throat. A streptococcus is the organism most frequently cultured from these throats.

THERAPY

Tonsillitis *per se* is rarely perhaps never, fatal but as an attack often ushers in a bout of rheumatic fever and as there are not infrequently complications, the disease merits serious attention. Perhaps the sulfonamides are used more often in tonsillitis than in any other entity but I know of no careful study which has shown this practice to be justified. Indeed the only controlled study which has come to my attention indicated just the opposite to be true. Rhoads and Afremow (1940) at the Cook County and Evanston Hospitals in Chicago treated 67 nurses who contracted tonsillitis while on duty. 31 received sulfanilamide and 36 did not. The drug did not reduce the severity of the symptoms, shorten the period of incapacity, reduce the incidence of complications or reduce the duration of the carrier state. Toxic manifestations other than the usual cyanosis occurred in one half the treated cases and in a few instances these reactions gave cause for genuine concern. These authors are unwilling to generalize from this experience but they conclude that surely no physician can be censured for withholding sulfanilamide in tonsillitis unless complications such as severe cervical adenitis, paranasal sinusitis, otitis media, mastoiditis or meningitis supervene. For the general principles of fever treatment the reader is referred to the article on the Common Cold. The vexed question of tonsillectomy is discussed in the article on Rheumatic Fever.

TRYPANOSOMIASIS

(*Sleeping Sickness*)

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever and since they do not nowadays raise problems in treatment for the general practitioner I shall no longer allot space to a consideration of them in this book.

TUBERCULOSIS

Nowadays we classify systemic infections with *Mycobacterium tuberculosis* into two distinctly different sorts according to whether the body is reacting to the first or the second assault of the organism. The lesion of first infection tuberculosis is usually microscopic in size and only very occa-

sionally gives rise to signs which may be detected roentgenologically in the lung or regional lymph nodes. Being also practically always asymptomatic it is not clinically diagnosed, but the positive tuberculin test indicates its presence. Typical disposition of the lesion, apparently accomplished through the natural resistance of the body, consists in deposition of lime salts within it until complete calcification has taken place. Within the core, however, tubercle bacilli may remain alive and virulent throughout the remainder of the patient's life. First infection tuberculosis is always the same, whether it took place last month or fifty years ago, the infant, youth and adult all react in the same way to the bacillus the first time it attacks. And the positive tuberculin test merely tells us that this reaction has taken place, i.e. that the individual has successfully withstood the primary assault (occasionally he does not so withstand it of course, but I can only present here the typical occurrence in the vast majority of instances). It does not indicate to us at what time in his life this assault took place, nor does it tell us whether he has the disease, tuberculosis. Most of us who must sadly confess to being middle-aged or worse are positive tuberculin reactors for the reason that in the years of our infancy and childhood little was being done to protect individuals from contamination with tubercle bacilli. Likewise in congested areas where little preventive work is going on today, the young are still almost 100 per cent tuberculin positive, but such high incidence of first infections no longer prevails widely throughout enlightened communities. The following are the figures on 97,548 tuberculin tests performed in my own state by the Wisconsin Antituberculosis Association through 1940 (kindly made available to me by Dr Florence MacInnis and Mr Harold Holand): birth to five years 77 per cent, five to nine years, 50 per cent, ten to fourteen years, 63 per cent, fifteen to nineteen years, 13.9 per cent, twenty to twenty four years 23.6 per cent, twenty five to twenty nine years 37.6 per cent, thirty to thirty four years 47.6 per cent, thirty five to thirty nine years 59.3 per cent, forty to forty four years 58.8 per cent, forty five to forty nine years, 70.5 per cent, fifty to fifty four years 63.2 per cent, fifty five to fifty nine years 74.1 per cent, sixty to sixty four years 66.7 per cent, sixty five to sixty nine years 61.1 per cent, seventy years and over, 10.0 per cent. These figures give the picture in a progressive agricultural industrial region with a population of average stability and not too heavy in the higher age groups. In a recent study of the student body at the University of Wisconsin, Stehm (1939) found that the incidence of positive reactors was lowest in those coming from the North Central (25.7 per cent) and Mountain States (26.3 per cent) and highest in those from the Desert States (84.6 per cent), the Eastern States (42.8 per cent), the Southern States (42.4 per cent), and foreign countries (67.6 per cent).

This is, then first infection tuberculosis, a condition that in itself is almost invariably harmless but that is nevertheless of the utmost importance to the individual in whom it exists since it makes him very vulnerable to the attack of the organisms the second time they assail him. The reason for this vulnerability is that during the course of the first infection, when the body was successfully protecting itself by throwing a wall of calcification around the invaders, the tissues became sensitized to the tuberculo-protein and a state of allergy was established quite comparable to that obtaining in the sufferer from ragweed pollinosis. In the latter, subsequent inhalation of

sufficient of the pollen touches off his typical hay fever attack, in the individual in whom the positive tuberculin reaction tells us there is a focus of first-infection allergy inducing tuberculosis, subsequent infection with sufficient numbers of tubercle bacilli containing the specific protein causes the appearance of lesions of such destructive nature that they can be arrested or entirely healed only with the greatest difficulty. It is this reinfection type of the disease with its well known signs and symptoms which is commonly designated "tuberculosis."

The source of the second infection may be exogenous (from bacilli distributed by some other individual in an infectious stage), or endogenous (the individual's own organisms having escaped into the blood stream a bronchus the subarachnoid space, or some other part of the body, through a defect in the walls which were built up around them during the asymptomatic conquering of the first infection). Endogenous reinfection is fortunately rare and usually occurs in infants or young children within three months from the time of the first infection, the most frequent clinical forms are the deadly tuberculous pneumonia, diffuse tuberculous meningitis, and miliary tuberculosis. Exogenous reinfections are the much more common, chronic and innumerable forms: pulmonary tuberculosis, bone and joint tuberculosis, peritoneal tuberculosis, skin tuberculosis, genito urinary tuberculosis, etc.

Pulmonary tuberculosis, the most common of all the types of reinfection tuberculosis, is of infrequent occurrence under the age of ten or eleven years but increases rapidly in incidence after that period. Therefore any child having a positive tuberculin reaction at the age of ten should be very carefully observed thereafter for the early signs or symptoms of reinfection. At Lymanhurst Health Center, in Minnesota, Chinn *et al.* (1930) made a ten year follow up study of 1218 children seven years of age at the beginning. 446 positive reactors without clinical lesions and 772 negative reactors. At the end of the study there were 9 cases of tuberculosis in the original positive reactors to 1 in the negative reactors and the mortality ratio between the positive and negative reactors was 38 to 1. The annual or semi annual roentgenogram is to be highly recommended since it will often detect a pulmonary lesion many months before other evidences of its presence appear. For those who present significant shadows Myer's (1930) recommendations are that the complete study then indicated include examination of the sputum and gastric contents for acid fast bacilli, periodic red cell sedimentation tests, observation for symptoms, examination for abnormal physical signs and frequent roentgen examinations to determine whether the shadow persists or changes in size.

In the code of Hammurabi, written at least as long ago as 2000 B.C. there are indications of a knowledge of tuberculosis. The classical Greek writers described its clinical features and were aware of its contagiousness but the latter point was not proved scientifically until Villemin devised his great experiments in 1865. The other outstanding advances of the nineteenth century were Laennec's remarkable studies with his new stethoscope, Louis' correlation of symptoms and pathology, Trudeau's pioneering in the sanatorium management of patients and finally in 1882 Koch's discovery of the causative organism. In the western world the tuberculosis death rate has been declining very markedly in recent times. Pronounced and widespread improvement in the economic status of the masses, combined most likely with

other factors which we do not understand, have been at work to lower the rate, but undoubtedly our own deliberate efforts have greatly contributed to bring about the result through (a) slaughter of cattle that are positive tuberculin reactors, (b) pasteurization of milk, (c) isolation of individuals with open and infective lesions of pulmonary tuberculosis, (d) education of the public to aid in preventing spread of bacilli, (e) modern collapse therapy which checks dissemination of organisms, (f) persistent efforts to detect and isolate unsuspected infective cases. In the United States the practical eradication of bovine tuberculosis (every county in the country now has less than 0.5 per cent of infected cattle) was accomplished only through the slaughtering of 4,000,000 tuberculous animals. Our death rate among whites is now the lowest in the world (Dublin, 1941), but in our 13,000,000 Negroes there is still a tremendous reservoir of the disease. Dublin says that their tuberculosis status today has not risen above that of the white population in 1910. The average death rate from the disease in Negroes is three and one half times that of the whites—but this is only the average, for in many cities the figure is even higher (more than eleven times the white rate here in Milwaukee). The fact that this disproportion is chiefly a reflection of the relative poverty of the Negroes only intensifies the disgrace. Epidemiologists say there should be 2 hospital beds per death, in the North and West there are 2.1, in the South 0.7. But the South is stirring and doubtless when next I come to revise this section of the book the situation will be vastly improved. Ringer's (1940) conviction that Negro doctors and nurses are needed to work among their own people in the South is certainly in line with the experience of some communities in which Negroes live in the North.

The death rate from tuberculosis is substantially higher in males than in females everywhere. Jews are relatively insusceptible to the disease. Throughout the Orient and in some portions of the tropics tuberculosis is still fatally rampant in all age groups, and even in the Occidental and enlightened lands it is still foremost as a cause of death in adolescence and early adulthood. In these latter portions of the world its supremacy is overthrown by heart disease, nephritis, cerebral hemorrhage and cancer only after the fortieth year of life. Says Opie (1935): "Since death with increasing age must be regarded as inevitable, tuberculosis may still be regarded as our foremost public health problem."

THE THERAPY

Sanatorium Regimen—"When we speak of the treatment of tuberculosis, especially pulmonary tuberculosis, we envisage sanatorium regimen, which is the basis of all treatment of the disease. Practically every other form of therapy is being applied by its practitioners to patients who are undergoing institutional care or some analogous substitute." Thus Krause in 1926, and I wish the reader to understand that in what follows I am always presupposing "sanatorium regimen," whether it be practiced in the home or in the hospital. Absolute rest in bed during the febrile periods, perhaps to be carried to the point of complete postural rest at times, as advocated by Webb and his associates, and to be followed later by carefully graduated exercises, a sufficient dietary composed of nutritious and palatable foods, the treatment to be carried out as nearly as possible in the open air, such changes of climate and general environment as afford the best oppor-

tunity of building resistance, and skilled medical supervision at all times—these are the important factors

Collapse Therapy—Artificial pneumothorax and the several surgical procedures for inducing partial or complete collapse of the diseased lung have rapidly advanced into the forefront of the battle against tuberculosis and yet I am unable to present to the reader a clear-cut statement of the indications and contraindications for the employment of these measures since those able to speak authoritatively are in disagreement. This much is certain that no one, not even any of the most ardent champions of collapse therapy, is today advocating the use of these measures indiscriminately in all forms of pulmonary tuberculosis. Ringer (1940) says that collapse therapy is employed as follows in three well known institutions: Hudson County, New Jersey, Sanatorium, 44 per cent; Sea View Hospital, Staten Island, N. Y., 40 per cent; Chicago Municipal Hospital 46.6 per cent. The average in 26 institutions in the South, of which he inquired was 47.1 per cent. It seems to me that, where not forced into the frequent employment of artificial pneumothorax as an expedient procedure when the number of available beds is severely limited, the best course for any practitioner is to be guided in his practice by those in his community who have had most experience with these measures—and to see to it always that the one he follows is a conservative fellow. Witness Hegner (1939), of Denver: "General rest and expectant treatment should be tried for a reasonable time, a period expressed in terms of weeks. As long as favorable progress is made, one should defer active therapeutic measures. When favorable progress is not made or ceases, active measures to secure the added benefits of local rest by some form of collapse therapy are promptly indicated. Collapse therapy is not a substitute for any of the older forms of treatment, it is an invaluable supplement to these when after a reasonable trial they have failed, or in the light of experience are destined to fail, to reestablish a resistance balance against the disease."

The earlier a focus not controlled by expectant treatment is attacked by the appropriate measure for collapse, the more certain, rapid and favorable will be the effect and the fewer the complications."

Heliotherapy—In his special article under the auspices of the American Medical Association Council on Physical Therapy, Mayer (1935) appraised the present status of light treatment about as follows: (a) Exposure of the entire body to carefully graded doses of sunlight, or proper artificial sources of such light, so that the visible ultraviolet and infra red rays are all utilized, is undoubtedly beneficial in tuberculosis of the bones and joints, peritoneum, intestines, lymph nodes and larynx. (b) Of the several forms of skin tuberculosis only lupus vulgaris responds specifically, scrofuloderma and erythema induratum favorably at times. (c) Postoperative sinuses are very responsive, fistulas often resistant. (d) Pulmonary tuberculosis *per se* is not an indication for light therapy. (Coulter and Carter [1935] agree on the basis of their findings) stationary pleural tuberculosis is often helped by it. (e) The treatment deserves a trial in genito urinary tuberculosis (Miller and Lustok, 1939 reported encouraging results from the use of ultraviolet ray therapy in genital tuberculosis in the male). (f) Ocular and aural tuberculosis respond infrequently, oral tuberculosis is most resistant.

Colonel Cooper (1938), summarizing the experience of the Army at its clinic for heliotherapy in Denver, is substantially in agreement with the

above. At this clinic, where treatment is apparently modeled on that of the famous Rollier clinic in Switzerland, the body is divided into the following six zones: ankles, knees, crotch, navel, nipple, chin, exposure being directed to these zones, front and back, in increasing numbers until at the fourteenth day the entire body, front and back, is exposed for the first time. But the exposures have progressed so gradually that this first exposure of the entire body is only for five minutes, front and back, not until the thirtieth day does complete exposure of front and back last a full hour.

Heliotherapy should be applied only under expert guidance, for an over exposure of a tuberculous patient to the sun's rays may be highly toxic and actually induce hemorrhage as the result of a nonspecific perifocal reaction.

Roentgen Therapy—Light therapy has almost completely superseded roentgen therapy nowadays, but, according to Mayer (see above), the latter may still be the treatment of choice in the infiltrative stage of lymph node tuberculosis. Employed together with heliotherapy, earlier results are often obtained in tuberculosis of the small bones, superficial joints, and skin. Hayes (1941), of the University of Minnesota Hospitals, says that it is the treatment of choice in pelvic tuberculosis of the female. But roentgen therapy should not be employed in any of these instances if there is also present an active pulmonary tuberculosis.

Tuberculin—The bright hopes which followed Koch's announcement of this substance as a specific remedy in 1890 were soon followed by disappointments so deep that many men today regard any and all types of tuberculin as absolutely worthless, a position which cannot be completely defended because a few careful users of the remedy have shown that it has a limited place in therapy. It is certainly in no sense a specific remedy and the number of cases in which it is indicated is very small. The recent study of Willis (1940) confirms one in the opinion that physicians who are not able or willing to make a special study of the treatment should never use tuberculin, the requisite guided experience cannot be gained from the pages of a text book.

Diet in General—The authoritative statement of Banyai (1934), here summarized, is corroborated by the experience of all specialists in tuberculosis: (a) the ordinary balanced house diet is adequate for the great majority of patients with pulmonary tuberculosis and, other things being equal, will restore the weight to normal, (b) increase in weight in those below par should be accomplished primarily by proper attention to the disease itself, (c) the use of strange, supplementary, concentrated foods to which the patient is not accustomed is not indicated, (d) overfeeding is both unnecessary and unreasonable and may be harmful in that extra weight taxes the pulmonary function, (e) milk may upset the digestive system and should not be forced as an accessory food, when included in the diet it is best taken in small sips after meals, (f) there is no proof that unusual quantities of eggs are helpful.

Special Dietary Factors—Cod Liver Oil—Despite the fact that cod liver oil has been used in the treatment of tuberculosis for about one hundred years, our knowledge of its value is still largely based on clinical impressions. The reasons for this state of affairs are: (1) that the oil is so objectionable in odor and taste, and often so disturbing to the appetite that

not many patients can be induced to take it faithfully, (2) that such effects as it may have are usually not seen until it has been taken for a period of many months or even years, and (3) the fact that not even its most enthusiastic champions would urge its use to the exclusion of the sanatorium regimen as adopted either in or out of a sanatorium. Evaluation under these circumstances is very difficult, and it is easy to understand how the drug has come to have its ardent detractors and its equally ardent but smaller number of supporters. The former point to the fact that use of the oil has been abandoned in most sanatoriums, while the latter cite the 'before and after taking' evidence of individual cases. And each side figuratively thumbs its nose at the other. The studies of Kramer, Grayzel and Shear (1929) and Pattisoo (1930) showed that whatever value there may be resides in the whole oil and not in the vitamin A and D ingredients. Cod liver oil concentrates, viosterol or viosterol reinforced cod liver oil are therefore not to be used in preference. Cod liver oil is best given two hours after a meal in a daily dose of 1 to 3 ounces (30-90 cc). Many individuals who are unable to take the distasteful substance in the beginning may be trained up to it by starting with very small doses. If both the oil and the spoon in which it is taken are kept on ice the odor is much lessened. Block has called attention to the fact that the eating of a banana immediately after swallowing the oil is most effective in overcoming the objectionable taste and odor and in preventing loss by vomiting. The U.S.P. emulsion, and the emulsions with malt and egg of the N.F., are potent and satisfactorily flavored, the N.F. emulsion with hypophosphites is an unnecessary preparation. The following prescription is a satisfactory working model for the writing of an emulsion, the rules being that there shall be at least one fourth as much acacia as oil to be emulsified and that the flavoring syrup shall not exceed 10 per cent of the total.

R. Cod liver oil	5iv	120 0
Acacia	5j	30 0
Syrup of thyme	5vj	24 0
Water to make	5viij	240 0
Label: One or more teaspoonfuls as directed		

Simple syrup might be substituted for syrup of thyme and flavoring accomplished by addition of 0.4 per cent (of the whole) of the oil of pepper mint, spearmint, lemon, orange or almond. The following formula for an aromatic oil is contained in the Pharmaceutical Recipe Book:

Glucose (saccharin)	0.5
Compound spirit of orange	20 0
Cod liver oil to make	1000 0

Vitamin C (Ascorbic Acid, Cerivamic Acid)—A number of independent observations in recent years have indicated that "exhaustion" of vitamin C occurs in tuberculosis and that the therapeutic use of the vitamin might be worthwhile. Sweany *et al.* (1941), of the Chicago Municipal Tuberculosis Sanatorium, have now reported an extensive study of the matter, 79 patients being studied for vitamin saturation and 232 in treatment. They found that exhaustion of this vitamin does occur and appears to be proportional to the

severity of the disease. Special diets high in vitamin C will prevent or relieve this unsaturation but in rare instances they found it necessary to administer a salt of ascorbic acid intravenously. Their tentative conclusion was that no patient should have less than the standard optimum dosage of 50 to 60 mg daily and that this quantity should be increased to as much as 200 mg daily in relationship to the severity, activity and duration of the disease. Frequently when the disease is far advanced patients deficient in vitamin C are benefited by being kept saturated with the vitamin as shown by a prolongation of life of the treated patients over the controls as well as slightly more favorable clinical and laboratory observations. Adequate vitamin C is therefore just one of the many factors necessary for a proper treatment of tuberculosis. No benefit was noted in an excess beyond saturation.

Insulin—A few years ago a wave of enthusiasm spread over certain circles in the profession for the use of insulin to promote hyperalimentation and weight gain in tuberculosis but the review of Allen (1936) showed that the many recorded disappointments and mishaps were sufficient to dampen quickly the ardor of most practitioners. This was only to be expected since insulin is a powerful agent and certainly not to be haphazardly used even in healthy individuals to say nothing of the tuberculous. However, that there is a class of patients in which its careful employment may be of some value has become evident since it will improve appetite and induce gain in weight in probably the majority of patients not extremely ill or moribund. Dosage with most observers has been between 15 and 60 units distributed throughout the day, the same precautions with regard to shock are of course to be observed here as in diabetes. Since the indications for the use of insulin in selected cases of tuberculosis are anorexia and loss of weight along with the frequently accompanying epigastric symptoms. Spellberg and Rosenblum (1936) made the sound point that it is illogical to use the agent in patients who are gaining weight even though they complain of unsatisfactory appetite but an occasional patient who is losing weight despite good appetite may benefit from insulin. They list the following definite contraindications: (a) laryngeal involvement when swallowing is painful; (b) gastro-intestinal tuberculosis with diarrhea which the increased food ingestion will aggravate; (c) extreme emaciation and exhaustion when the patient needs help in feeding and is prone to develop severe reaction.

Salt free (Gerson, Sauerbruch, Hermannsdorfer) Diet—These diets were evolved in an effort to change the nature of the soil in which the tubercle bacillus lives though they came originally into use following the fortuitous discovery by the principal proponent (Gerson) of improvement in a case of lupus in whom a salt free diet was being used for another purpose. The good results in many types of tuberculosis reported by Gerson have not been susceptible of duplication by most other observers but Dr Gerson was still indefatigably pursuing the subject in Paris before the outbreak of the second World War. I think it is now universally acknowledged that this type of dieting is often of great cosmetic benefit in lupus vulgaris and that often times in renal and sometimes in bone and joint tuberculosis it is worth the trial. Pulmonary cases unresponsive to other treatment may occasionally be benefited. The diets are quite objectionable to the patient and are so complex in their original form that they are at present looked upon as suitable only for use in institutions where there is complete control of patients and

expert dietary supervision. However, Banyai (1934) found that the regular house diet can be made to serve the purpose very well through modification as follows: (a) add no salt to dishes and omit canned foods of all kinds as well as smoked and spiced meats, sausage and ham, smoked and salted fish; (b) season with curtasal, a nonsodium and chlorine bearing salt substitute; (c) give 7 drops of viosterol and 15 grains (1 Gm) of calcium lactate *thrice daily*.

Creosote and Guaiacol—Creosote and guaiacol have been before the profession for a great many years and have failed to establish a place for themselves. In 1938, the Council on Pharmacy and Chemistry reviewed the subject and decided to drop these compounds from N N R. In 1939, Fellows published studies which failed to show any advantages derived from the use of one of the chief preparations in pulmonary tuberculosis. I shall therefore no longer continue a discussion of these drugs in this book.

Cod liver Oil as Topical Application—Banyai (1940) made topical application of this oil in 270 cases; in brief summary he found: (a) favorable effects in pharyngeal and laryngeal ulcers and in laryngeal infiltrations with vegetative granulation, but not if there is marked laryngeal edema; (b) tuberculous empyema in the absence of bronchopleural fistula responded well to aspiration of pus and replacement by the oil; suppurating lymph nodes were similarly treated with satisfaction; (c) in the form of eye drops the oil was unsatisfactory in tuberculous keratitis but of use in phlyctenular conjunctivitis and keratoconjunctivitis cases; (d) the oil was of some value in cold abscesses secondary to bone tuberculosis, in fistulas originating from tuberculous epididymitis and in ischio-rectal fistulas; (e) the results were very good in scrofuloderma and in lupus vulgaris. Fitzgerald and Banyai (1940) have satisfactorily applied the oil in 4 cases of oral tuberculosis.

Miscellaneous Remedies—The following agents or methods have all been considered at one time or another to exert some more or less specific action, but none of them at present seem to merit a place in the discussion of practical phases of therapy in tuberculosis. Dreyer's defatted antigen, gold sodium thiosulfate (sanocrysin), calcium salts except in the treatment of intestinal tuberculosis (qv), iodine or the iodides, sodium morrhuate, Spengler and Spahlinger treatments.

Fever and Night-sweats—Under the sanatorium regimen which is being presupposed throughout this entire discussion, these two symptoms usually do not persist in aggravated form long enough to warrant a resort to drugs in their correction. However, when the former is felt to be excessively wasting the patient by its daily high rise it is nearly always possible to forestall it by the use of 5 to 10 grains (0.32–0.65 Gm) of aspirin or phenacetin, 5 grains (0.2 Gm) of acetanilid or 5 grains (0.32 Gm) of amidopyrine (see Agranulocytosis for toxicology of the last drug). Night sweats are more difficult to treat. They can sometimes be prevented by the use of atropine sulfate in a dose of 1/200 to 1/100 grain (0.00052–0.00065 Gm), but frequently at the price of an increase in cough and restlessness also agaricin may be used in ½ grain (0.032 Gm) doses in pill or capsule, not to exceed three of which should be given in the twenty-four hours, but this drug is extremely unreliable in its action. Hare wrote enthusiastically of camphoric acid in a dose of 20 to 30 grains (1.5–2 Gm) an hour or two before the sweat is expected, repeating the medication once in obstinate cases. He used the following formula:

R Camphoric acid	℥iv	16 0
Alcohol	℥ij	60 0
Mucilage of acacia	℥iij	90 0
Syrup of orange to make	℥vj	180 0
Label Dessertspoonful (8 0) to a tablespoonful (16 0) one hour before sweat is expected.		

The above is difficult to prepare and the following is simpler

R Camphoric acid	℥iv	16 0
Compound tincture cardamom to make	℥vi	180 0

An alcohol rub at bedtime or a sponge bath with tepid water to which has been added 15 grains (1 Gm) of alum per ounce, is also sometimes effective in preventing mild sweats

Cough—Here again, as in the case of fever and night sweats, the rest which is so important a part of the sanatorium regimen, is the most valuable remedy of all. Many patients succeed in training themselves to control this symptom remarkably well only permitting themselves to indulge in a thorough cleaning-out cough in the morning, but when a wracking cough is disturbing the patient's rest both night and day, some attempt must be made to check it. The reader is referred to the discussion of cough in the article on Common Cold. In selected, very distressing cases in which it is feared that persistent coughing might lead to spontaneous pneumothorax or some other serious complication, Banyai (1934) resorts to repeated inhalations of carbon dioxide (10 per cent) and oxygen and finds the measure often effective in promoting the removal of thick, sticky mucous secretion from the lower respiratory passages.

Hemorrhage—Keep the patient as quiet as possible with the head propped in such way that blood will easily flow out of the mouth. Mayer (1935) advises against the use of morphine as it favors spread of the disease through retention of infectious clots. Goldman (1936) says that codeine should be given first and that if morphine finally becomes necessary no more than a single dose of $\frac{1}{2}$ grain (0.01 Gm) should be used. Ice bags on the chest over the suspected site of the hemorrhage are reassuring, small bits of ice are usually given to be swallowed. Sand bags on the chest and against the side help to accomplish partial immobilization. In some instances one of the forms of collapse therapy is necessary—Matson (1940) says hemoptysis is a mandatory indication to establish an artificial pneumothorax at once if it is possible to determine from which lung the blood is coming. Amyl nitrite or nitroglycerin is sometimes used to lower blood pressure. But I think this type of therapy illogical in a patient threatened with shock. Several men have reported the successful use of Congo red. Hemostatics of the usual tissue extract or serum types are of no value. Berghausen (1937) has reported 2 cases in which intravenous injection of 30 Gm of neocasia in 500 cc of physiologic saline was followed by cessation of the bleeding.

In patients who have a long period of blood spitting after the acute hemorrhage, Gordon, Roark and Lewis have used 10 units of parathyroid extract every second day for two or three weeks, Solis-Cohen and Githens recommend hydrastinine hydrochloride, $\frac{1}{2}$ grain (0.015 Gm) hypodermically or $\frac{1}{2}$ grain (0.03 Gm) by capsule, three times daily. I doubt the rationale of

both these measures. Following cessation of the bleeding, diet is restricted to cold dishes and drinks for a while. The use of cathartics or enemata to prevent straining at stool is advisable in some instances.

Care of Digestion—This is extremely important, for the majority of sufferers from pulmonary tuberculosis have some form of indigestion, it is best accomplished by enjoying slow and thorough mastication and complete rest both before and after meals. Sodium bicarbonate in a dose of 15 grains (1 Gm.), or $\frac{1}{2}$ drachm (2 cc.) of the aromatic spirits of ammonia, the former dissolved in warm but not hot water and the latter to be well diluted before taking, will usually dispose of postprandial distress, or, if these fail, the opposite treatment with dilute hydrochloric acid in a dose of 15 minims (1 cc.) may be indicated. It is extremely doubtful whether pepsin or pancreatin is of any value here. Such simple remedies as the drinking of a little hot water before meals or placing an ice bag on the abdomen will often relieve nausea. If there is vomiting and much distress during the day an evening lavage of the stomach, using preferably the duodenal tube, may give relief for the night. To stimulate a lagging appetite any one of the following excellent U. S. P. stomachic mixtures with a dose of 1 teaspoonful before meals, is of value: compound tincture of cardamom, compound tincture of gentian, compound tincture of cinchona, or the tincture of nuxvomica in a dose of 15 minims (1 cc.). Also "tonic" mixtures should not be overlooked, arsenic is of especial value as an appetite stimulator. Some such capsule as the following may be used for a short time.

R	Arsenic trioxide	gr ss	0 03
	Extract of nuxvomica	gr v	0 32
	Quinine sulfate	ss	2 00
	Make 40 capsules		

Label: One, later two capsules three times daily after meals

The full tonic dose is contained in 2 capsules, but the precaution of giving only 1 the first day will make possible early detection of quinine idiosyncrasy.

Pleuritic Pain—The pain accompanying pleuritic inflammation is often times very severe and greatly retards the patient's progress. A few cases will respond favorably to counterirritants. Two of the small mustard plasters obtainable at drug stores should be used end to end under the arm, so that one extends toward the nipple region in front and the other over the lower part of the scapula behind. Adhesive plaster strapping is more often effective, applying the straps to the side with the patient in the sitting position and holding the breath after a forced expiration. In an unfortunately large number of cases, however, it is necessary to resort to opiates. Swetlow, in 1926, reported in detail on 5 cases in which he had succeeded in relieving the pain by the injection of 80 per cent alcohol into the intercostal nerves close to where they emerge.

Laryngeal Pain—Vocal rest is sheet anchor therapy, collapse treatment valuable as both preventive and curative agent in laryngeal tuberculosis. For the relief of the excruciating pain which often accompanies deglutition cocaine is used in a spray of 1 to 4 per cent, this is always to be considered dangerous, however. Orthoform which is an insoluble anesthetic, may be blown into the larynx, but Lockard prefers to use it in the form of an emulsion. He gives the following formula.

Orthoform	12 parts
Menthol	1 part
Almond oil	30 parts
Yolk of egg	25 parts
Water to make	100 parts

This emulsion is too heavy for use in an atomizer, but it can be self administered through the use of a Yankauer laryngeal medicator. Iodoform is also frequently used by insufflation, but a small amount of talcum must be added to give weight to the otherwise too light powder. The drug seems to be antiseptic in its own peculiar way and somewhat anesthetic, though it is wise to precede the insufflation with a spray of cocaine to prevent coughing. A number of writers advise the addition of morphine to the powder mixture. Hare used 1/16 grain (0.004 Gm.) to each drachm of iodoform. Another mixture sometimes successfully used is known as Lake's pigment, the formula of which is

Lactic acid	50 0
Solution of formaldehyde	7 0
Phenol	10 0
Water to make	100 0

The phenol in this preparation acts as an anodyne but it is usually necessary to precede the first few applications with cocaine. Ulcers and granulations may also be touched with 5 to 10 per cent formalin in glycerin, preceded by a cocaine spray. Lukens has stated that the local application of chaulmoogra oil, without preliminary cocaineization, exerts an analgesic action on the larynx which becomes more complete after repeated treatments. Alloway and Lebensohn and Van Poole have in some measure confirmed Lukens but Peers and Shipman warn that the general condition of a febrile patient may possibly be made worse by these treatments. Wilkinson (1932), and Stevenson (1933), did not obtain the satisfactory results they had hoped for but the latter, reporting again in 1937, found the treatment beneficial in a large proportion of patients when he changed from Indian to Burmese oil, as recommended by Lukens.

Banyai (1938) introduced the method of spraying the larynx three times daily with cod liver oil from an ordinary atomizer, the oil must be warmed before use and the treatment is best given after meals. Banyai's results were good and so too were those of Fox and Wigglesworth (1939). I know other men who have been using this measure with satisfaction.

Galvanocautery (Weidman and Campbell, 1939), alcohol injection of the superior laryngeal nerve, actual section of the nerve (Raine and Banyai, 1932 inject alcohol and then crush and sever the nerve), ionization (Cotton Cornwall, 1938) and tracheotomy are all employed successfully at times by qualified experts.

Here is a practical point which Dundas Grant (1932) has called to the attention of the profession. "I wish, however, to indicate a cause of what patients call pain," the relief from which is anxiously desired. In reality it is a painful burning stiffness of the pharynx caused by the drying and inspissation of mucus on the back wall and is experienced chiefly on waking. Patients have frequently described the discomfort as severe pain and

have been delighted to have it removed by gargling with a little bicarbonate of soda in water, warm if possible, otherwise cold. Such a solution can be put into a thermos flask at night so as to be ready for use when the patient wakes up. I am sure that this condition is overlooked while deeper lying sources of pain are being sought for. It seems a trifling method of treatment, but it gives great relief and is, of course, available to any practitioner if he only keeps the condition in mind and looks for it."

Intestinal Symptoms.—Until the appearance of Sartorff's report, in 1918, on the use of calcium chloride as a palliative agent in the treatment of intestinal tuberculosis, we were practically helpless in the presence of the severe abdominal pain, exhausting diarrhea and tenesmus suffered by patients who are the victims of this type of the disease though it has long been recognized that in some cases surgical procedures are indicated. The value of heliotherapy, more recently recognized, has already been pointed out. Pneumoperitoneum is also sometimes of value in selected cases. The various astringents are practically valueless, and dietetic treatment, even when faithfully persisted in, succeeds only exceptionally. The excellent results reported by McConkey (1930), who administers $\frac{1}{2}$ ounce (15 cc) of cod liver oil floated on 3 ounces (90 cc) tomato juice in a small glass, the dose being taken ice cold immediately after each of the regular full hospital meals, have not been confirmed under satisfactory control conditions (Steinbach and Rosenblatt, 1935), nevertheless Banyai (1940) says he frequently obtains good results with this treatment. The opiates are, of course, somewhat effective, but they must be used in very large doses and when they are intermitted the symptoms are oftentimes much aggravated. In calcium chloride, however, we have a really valuable addition to our armamentarium. It is usually given intravenously, in a dose of 5 to 10 cc of a 5 to 10 per cent solution (sterilized in the autoclave) at intervals of three to seven days; this dose may be repeated as long as necessary, it would seem. Fishberg particularizes as follows:

"When the diarrhea in a tuberculous patient is due to dietetic indiscretions, to the catarrhal condition of the intestinal mucous membrane, or to slight intestinal ulceration, an intravenous injection of 5 cc of a 5 per cent solution of calcium chloride will give prompt relief. When, however, the intestinal symptoms are due to extensive ulcerations—especially to amyloid infiltration of the intestine—the chances of attaining relief of the pain and annoying diarrhea are remote. Similarly, when the abdominal pains are due to irritation of the intestinal mucous membrane by the contents of the intestine, relief may be attained by intravenous injection of calcium chloride. When, however, the pains are due to localized peritonitis over deep intestinal ulcers, or to peritoneal adhesions which are not uncommon in tuberculous subjects, calcium chloride is impotent to give relief."

Cantarow says that good results may be obtained in less urgent cases by giving calcium by the mouth, avoiding the irritating chloride, calcium gluconate, 60 grains (4 Gm), calcium lactate, 30 grains (2 Gm), or aromatic chalk powder, 30 to 60 grains (2 to 4 Gm), three or four times daily. Pisani (1939) prefers intramuscular injections of calcium gluconate. Hardt *et al* (1939) feel that no one method of administration has particular preference over another, in their experience ultra violet irradiation seemed to increase slightly the beneficial effect from calcium.

Terminal Opiates—In the terminal stages of many cases the suffering is very severe. Here the opiates in full doses are oftentimes truly a god send for they enable us to make the last days of these poor unfortunates much less terrible than they would otherwise be. However, the question of expediency often arises, for opium many times prolongs life in such patients and a truly immense quantity of the costly drug may be required before the awful end is reached.

Psychotherapy—There is so much talk nowadays of the great value of this method—as though it were *new*, indeed!—that I fear some of us are beginning to believe all of it. Certainly we accomplish very little when our aim is only to gloss over a real psychological conflict with a mere grin. I know not a few persons who revolt temperamentally against the sort of planned cheerfulness that is current. Perhaps the reader may feel that they are then almost certain to die if they come down with tuberculosis—and it may be that they are!

PROPHYLAXIS

Since 1922, large scale vaccination of infants against tuberculosis has been going on in France and in portions of some of the other Continental countries, the aim of this prophylactic attack being not to produce permanent immunity but only to support the child's reactions during the period when natural immunization is taking place. The vaccine used is made from cultures of living bovine bacilli that have been attenuated by growing them for years on bile potato medium (*Bacillus Calmette Guérin*, or BCG), it being claimed that these organisms are still capable of stimulating antibody production though they have lost their power to produce tuberculosis either in a general or local form. An enormous literature has accumulated upon the subject, which remains highly controversial, the especially interested reader will find the following to be recent significant publications: Guérin (1935) France, Kayne (1936), England, Goodwin (1936), Levine *et al* (1938), United States, Hopkins (1941), Canada. Here in our own country, Park, Kereszturi and their associates are attempting a thorough study of the matter under conditions of adequate control, in the outcome of which all serious students of the subject are of course much interested. Upon the whole, however, here in America—and I believe I may say as much of England also—the attitude is still one of very cautious skepticism. I shall attempt to expose the chief roots of our conservatism in the following paragraphs.

(a) Careful and competent statistical analysis of the French data has failed to convince us that human tuberculosis is effectively prevented by this method.

(b) The organism is admittedly capable of producing lesions in the animal body, from which it can be recovered, but it is denied that it can establish active centers of tuberculosis or is able to set up progressive tuberculosis on reinoculation into fresh animals. We do not consider this point of avirulence proved.

(c) In Lübeck, during three months in 1930–1931, there were 68 fatalities in infants which were directly traceable to the vaccine. It seems now to be established definitely that the culture sent from Paris to Lübeck was not virulent, but something happened to the culture in Lübeck, though it was never possible to determine what that something was. It is difficult

to forget Lübeck, and we want assurances that under proper safeguards (which no one can as yet define) the thing will not occur again.

(d) In France there is increasing recognition of the fact that the vaccinated need just as much protection against contamination from openly tuberculous individuals as the nonvaccinated. Wherein, then, lies the advantage of vaccination?

(e) A positive tuberculin reaction is admittedly the only evidence that vaccination has been successfully accomplished. But to us the positive tuberculin reaction indicates a state of allergy and connotes other things being equal, development of the reinfection type of tuberculosis when the individual is subsequently assailed by the bacillus of tuberculosis in adequate numbers. It would seem that the advocates of BCG vaccination rush in to induce in early infancy the same state of allergy which it is the object of our utmost endeavor in this country to prevent.

(f) At the beginning of this present article on tuberculosis I have offered a brief résumé of the prophylaxis of the disease as practiced in America: application of the fine tooth-comb method of finding infectious cases in order that, through their isolation, infants and children may be protected from acquiring first infection tuberculosis as long as possible. The method is apparently efficacious though costly and not giving any very bright promise of ever eliminating the disease entirely. But hasty adoption of BCG vaccination in the present state of knowledge regarding the true value of this 'preventive' measure might really be comparable to swapping horses while crossing a stream.

The outbreak of World War II terminated for the time being some experimental studies with a vole vaccine in England which were reported to be yielding more promising results than with any methods tried up to this time.

TULAREMIA

(Rabbit Fever)

Tularemia is an infectious disease of wild rabbits, squirrels, mice, rats, muskrats, beavers, woodchucks, opossums, skunks, raccoons, game birds and doubtless many other animals; cats, dogs, coyotes, cattle and sheep are already partially convicted. There is some presumptive evidence that wild rabbits can convey the disease to domestic poultry. Infection from handling pelts and man to man transmission are both exceedingly rare. Originally considered to be confined to the United States where it was first described, it is now recognized that tularemia is probably world wide in its distribution. Human beings contract this malady while dressing the carcasses of infected animals, or through the bite of one of the several flies and ticks which act as vectors, and also through ingestion of the insufficiently cooked flesh of infected animals. The usual incubation period seems to be two to five days though it varies from one to ten days. The causative organism, *Pasteurella tularensis*, was discovered by McCoy and Chapin in 1912, but the disease in man has been definitely known to be caused by the same organism only since the work of Francis in 1919.

The onset is sudden, with chills and fever, pains all over the body, vomiting, sometimes diarrhea and often cough, and prostration. Pneumonia of broncho or lobar distribution is an early manifestation in many cases. Usually after the first few days of fever there is a remission of a few days and then another rise which persists, with marked daily remissions of the septic type, until it gradually declines in two to four weeks. In addition to the systemic symptoms, there is usually pustulation and finally ulceration at the site of infection, and the glands draining the area become swollen and painful. In more than half of the cases they too break down but sometimes only during a recurrent adenopathy several months or years after apparent complete recovery. Foshay (1949) says that in about 8 per cent of instances bubo formation does not occur and that in these instances there is also very seldom any discoverable primary lesion. During the second week (occasionally not until the third or fourth week) the serum agglutinates *P. tularensis*, the intradermal test may be positive a week earlier. In laboratory-contracted cases the local and glandular symptoms are absent, probably because the organism is ingested in these instances. Convalescence is usually very protracted. Relapses sometimes occur several months to years after apparent recovery, but no true second infection has yet been recorded. Mortality is considered to be about 6 per cent, most deaths occurring at the beginning of the third week in cases which have become of a typhoidal type and in which pneumonic manifestations have been prominent.

THERAPY

In April, 1940, the United States Public Health Service stated that there is no specific treatment for tularemia, a statement which was doubtless carefully considered before it was made. However, Foshay continues to make out a case for the ability of his antiserum—now available from both horses and goats—to modify the course of the disease. His most recent (1949) report is in the form of a compilation of results obtained by many widely scattered physicians, using the serum in 600 cases with 518 untreated controls. I am obliged to confess that his handling of the data is completely confusing to me, so I can only repeat his statement that his statistical studies confirm the clinical opinion that serum therapy effected significant changes in the course of the disease and in the mortality rate, the most favorable modifications being observed in patients who were treated before the thirteenth day. As was to be expected, serum sickness occurred in slightly over half the cases. Foshay does not advise use of the serum as a routine measure, his indications are the presence of tularemic pneumonia, the typhoidal state, if confusion and delirium supervene, and if there is coexisting heart disease. Dosage for adults is 30 cc intravenously, repeating in eight to twenty-four hours as indicated, in fulminating cases 60 to 90 cc should be used for the first dose. Reports of successful treatment with quinine, the intravenously injected dyes (Lovia [1941] gave acriflavine intravenously in dosage of 100 mg in 250 cc saline), iodides, neoarsphenamine, etc., are still very scattered. Curtis (1939) reported the successful use of sulfanilamide in 1 case, but Terry and Reichle (1949) used it in 2 cases which went on to fatal termination, I know of a number of unreported instances in which the drug was used unsuccessfully. Moss and Weilbaecher (1941) say they have seen striking improvement

in "several" cases in which they used sulfathiazole Winter *et al* (1937) thought that the twice daily intravenous administration of 20 grains (1.2 Gm) of sodium salicylate in 1 ounce (30 cc) of distilled water made their 4 patients with pulmonary involvement less "toxic", all the patients recovered—in one of these cases, in which there were meningeal symptoms they felt that daily spinal drainage was definitely beneficial. Convalescent serum has not been considered to be of value up to the present time, but Badger (1939) says Foshay has told him of a case which was treated "as effectively by immune serum as by antiserum." The usual palliative measures are of course indicated.

All who have had experience in this disease are in agreement that the broken-down lymph nodes should be undisturbed beyond the use of hot wet dressings. Excision is absolutely contraindicated and no abscess should be incised until it is about to break through the skin.

TYPHOID AND PARATYPHOID FEVERS

(*Enteric Fever*)

Typhoid and paratyphoid fevers are acute infectious diseases caused by *Eberthella typhi* and *Salmonella paratyphi-A* and *S. schottmulleri-B*. They are unquestionably separate diseases since an attack of any one of the three does not confer immunity against the other two, a fact which is also true in regard to artificial immunization, nevertheless, they will not be considered as separate clinical entities in this book for the reason that in their symptomatology (save for the relative mildness of the paratyphoids) and their therapeutics they are one and the same. Serologically and bacteriologically they can be distinguished the one from the other, at the bedside this differentiation can never be made with certainty. I shall discuss the three under the single designation "typhoid fever."

In typhoid fever the attack is essentially upon the lymphoid tissues of the body, being especially marked by enlargement of the spleen and hyperplasia and ulceration of the Peyer's patches in the intestine. The majority of those who fall ill of this disease are between the ages of fifteen and thirty. There is usually a prodromal period of about a week, during which there is malaise, headache, loss of appetite, and pains all over the body. Then the patient goes to bed and the attack is looked upon as definitely established. The fever is considered to be typical in that it rises to its peak—which may be as high as 105° or 106° F (40.5° or 41.0° C)—by the end of the first week, remains at this level for a variable period but usually one to two weeks and then falls gradually during a length of time which is usually twice that required for it to rise, throughout the entire course of the fever there are daily morning remissions of one or more degrees. It should be remarked that there are many variations from this typical fever picture. The pulse, too, is characteristic in that it is much slower than one would be led to expect by the height of the fever and nearly always contains at some time a dicrotic wave. At about the end of the first week the so-called "rose spots" appear usually

only on the abdomen, in crops of 10 or 12. Though present at some time during the course of perhaps 95 per cent of cases it is nevertheless certain that true typhoid does occur without the appearance of these spots, I shall never forget a young practitioner who dramatically renounced a medical career because in one of his early cases a consultant overbore him by diagnosing typhoid fever *without* rose spots. The blood pressure is low throughout the attack. The tongue is clean and red around the border including the tip, and heavily furred in the center. Nosebleed and bronchitis are frequent early symptoms. Distention of the abdomen practically from the beginning is regarded as very characteristic of typhoid, but with the more ample diet now in vogue this symptom is not regularly seen. Constipation is the rule, when diarrhea occurs it is usually of the "pea soup" variety. Delirium, usually of a canny rather than a violent type, is frequent. Prostration is always great and in severe cases progresses to the state of stupor known as the "typhoid state," during which the patient lies in a low muttering delirium, eyes open and staring and hands ceaselessly pulling at the bedclothes. The progressive secondary anemia, so common in typhoid, is not so severe nowadays as it was during the era of starvation treatment. At the height of the disease there is nearly always a leukopenia. The specific agglutination of the organisms by the patient's serum is of diagnostic importance, but the worth of this Widal reaction is considerably lessened by the frequency with which it is negative until as late as the third week and the instances, few to be sure, in which it does not become positive at all. The bacilli are themselves present in the blood during the first week, after that they appear in the stools and often in the urine as well.

The principal complications of typhoid fever are intestinal hemorrhage and perforation, pneumonia, venous thrombosis, and ulcerative laryngitis. Relapses, in which all the symptoms reappear after a brief asymptomatic period, are frequent, they are usually less severe and of shorter duration than the initial attack. The mortality from typhoid is now about 10 per cent under the best conditions. Perhaps 60 per cent of the fatalities are due to toxemia, 15 per cent to perforation and subsequent peritonitis, 10 per cent to hemorrhage and 10 per cent to pneumonia, true typhoid meningitis is practically always fatal but this complication is extremely rare.

Case reports of atypical types of typhoid fever have appeared in recent years: typhoid pyelonephritis without symptoms referable to the intestinal tract (Rimmonn, 1938), uterine bleeding as a prominent symptom (Wofford *et al.*, 1938, Lantin *et al.*, 1939), cases in which the symptom of agranulocytosis or of purpura predominated (Lantin *et al.*, 1939), cases with no evidences of intestinal involvement at autopsy (Lantin *et al.*, 1939). Malbin (1940) reports that the vast majority of cases occurring after partial or complete vaccine immunization, seen by him during an outbreak in Spain, showed abbreviated or otherwise atypical courses. Dietrich's (1937) analysis of 60 cases in infants and children shows a characteristically abrupt onset in them, the frequent appearance of neurologic symptoms, and a shorter course and lower mortality than in adults. Diddle and Stephens (1939) describe a case of probable intra uterine typhoid fever in a baby born of a mother convalescent from the disease.

Typhoid fever is undoubtedly a very old disease, but it was long confused with typhus. The belief was formerly held that certain parts of the

tropical portions of the globe were free from the disease, but more careful studies of the fevers prevailing in these regions have shown them to be the same typhoid which ravages the rest of the world. The human body is the only natural habitat of the causative organisms and all cases are caused by contact with the feces or urine of an infected individual, whether he be actively infected or a "carrier." This contact may be direct or indirect through a contaminated water or milk or ice cream supply, by the ingestion of food over which flies have dragged their infected filth, or the eating of oysters which have been infected in their feeding or fattening beds, or even through the medium of ingested dust—this latter method of infection was held responsible for many of the cases in the British army during the Boer War. Being a filth-borne disease it is to be expected that modern sanitation would have greatly lessened its incidence, and so it has, indeed, the decrease in typhoid in this present century is one of the things of which medical sanitary science has most reason to be proud. For nearly a decade now the death rate per hundred thousand in representative large cities in the United States has been below 10, whereas in 1910 the rate was slightly above 200, in a few cities in the South, however, in which the former rate was as high as 350 to 500, it is still between 30 and 40.

Typhoid fever, which increases in incidence after June to a peak in late fall and early winter, is by no means the thing of the past that it is unfortunately represented to be in some quarters. How this pestilence is lurking about all great cities, ready to swoop down upon the inhabitants when the guard is the least bit relaxed, was amply shown in the Montreal epidemic of the spring and summer of 1927. In a certain portion of that city of approximately a million inhabitants, during a considerable period of time the raw milk from a district outside the city in which sanitary conditions were unsatisfactory was allowed to be distributed without being adequately pasteurized. The result was that there developed in the city, between the approximate dates of March 1st and September 1st, a total of 5014 cases of typhoid, 500 of which terminated in death. More recent epidemics have been those at Bournemouth (1936) and Croydon (1937), in England, and a severe one in a state hospital for the insane in Illinois (1939). Trailer camps and eating places along much travelled highways have also scattered cases widely throughout our country in a few instances in recent years. Harvey (1937) feels that perhaps some cases of infection with *Salmonella suspestifer* are mistakenly diagnosed paratyphoid fever because of the frequency with which cross agglutination in test sera may occur.

THERAPY

Dietetics.—Typhoid fever has greatly changed in my time—which is an astonishing thing since no specific remedy has been added to the armamentarium. But changed it has, for I well remember that during my childhood which was spent in a large city in Kentucky, it was quite as usual for a number of relatives and acquaintances to be hovering about the edge of one's consciousness as gaunt and tottering specters who were "recovering" from typhoid, as it was for all of us to be dosed with quinine during a part of each year. I was twice attacked by the disease (typhoid or paratyphoid? Widals were only beginning to be done then) in my youth and twice, though

neither attack was very severe I had to learn all over to walk again. Where are the convalescent ataxics of yesteryear? And why are we so seldom able to show to our students of today the wasted individual with grotesquely protuberant abdomen exhausting himself in hallucinatory delirium or worse still lying in the low distressing typhoid state? Perhaps the organism is becoming less virulent or mass immunity is being built up but I believe that the true answer lies in the changed attitude toward diet in the treatment of this dread disease. All of which is but a verbose preamble to the following statement: *the introduction of the full diet in the therapeutics of typhoid fever is the greatest contribution of all time toward the therapeutic control of the malady*

TABLE 6—TYPHOID DIET WHICH WILL FURNISH 3000 CALORIES

Breakfast	Calories.	3 to 4 P.M.	Calories
Farina (4 tablespoonfuls cooked)	100	Tea 150-200 cc	00
Toast (1 slice, 30 Gm before toasting)	80	Lactose 50 Gm (1½ ounces)	200
Cream 100 cc. (3½ ounces) 20 per cent which is approximately the same as the top 4 inches from a quart bottle of milk that has stood at least six hours	200	Sugar 5 Gm	20
Butter 8 Gm	60	Cream 30 cc. (1½ ounces)	100
Lactose 40 Gm (1½ ounces) To add lac- tose to milk, boil 15 Gm in 30 cc of water cool and add to milk	100	Crackers, 3 unsalted or 2 soda, toasted	75
Sugar 20 Gm	80	Butter 8 Gm	62
Coffee 1 large cup	00	Supper	
10 to 10 30 A.M.		Rice 25 Gm (1 ounce) boiled	100
Milk 200 cc. (8½ ounces)	140	Milk, 100 cc (3½ ounces)	70
Cream 50 cc (1½ ounces)	100	Toast, 30 Gm (1 slice)	80
Dinner		Butter 8 Gm	60
Eggs, 2	150	Sugar 5 Gm (for cereal)	20
Potato, 1 medium about	100	Cream 60 cc. (2 ounces)	120
Bread, 1 slice or roll 1	80	Orange, 1 sliced	100
Butter 30 Gm (1 ounce)	254	Sugar 5 Gm (with orange)	20
Apple, 1 medium sized (pared and cored)	254		
Sugar 15 Gm (½ ounce)	60	8 to 9 P.M.	
(Potato baked served with butter Apple baked with 15 Gm sugar and about 8 Gm butter. Some patients will eat more butter if the unsalted is used)		Cocoa, 5 Gm	25
		Sugar 10 Gm	40
		Milk, 150 cc. (5 ounces)	105
		Cream, 30 cc (1 ounce)	60
		Lactose, 25 Gm.	100

The mind at once leaps to the question how has it affected mortality? This is of course very difficult to answer statistically, though the studies of Warren Coleman and others seem quite convincing but it is the almost unanimous clinical impression that full feeding has had much to do with the reduction in the death rate which has occurred in the last few years. Certainly the severity of the symptoms is greatly lessened extreme tympanites is unusual and when it occurs can often be overcome by a proper adjustment of the diet diarrhea often yields in the same way and constipation on the other hand is less stubborn because there is actually considerable food residue present to be propelled through the bowel both delirium and stupor are

modified, bed sores are practically a thing of the past, anemia is scarcely ever so profound as on the starvation diet, and what is best of all, the patient leaves the bed very little more wasted than he entered it, thus tremendously reducing the period of convalescence. And if it cannot be proved that the high calorie diet has reduced the incidence of hemorrhage and perforation it certainly cannot be proved that it has increased it either. Relapses seem to be more frequent, however, under the new treatment.

Proper feeding, then, is the most important element in the treatment of typhoid fever. Indeed, the old difficulty of devising means of reconciling the patient to the exclusive milk diet which was imposed under the old régime has given way to a diametrically opposed problem, namely, that of getting as much food into him as it is now considered desirable for him to take. Four thousand calories per day is perhaps the optimum amount if we are entirely to prevent loss of protein from the tissues, but it is almost impossible for any but convalescent patients to accomplish the daily consumption of this much food, 3000 calories, however, should be possible with skilful nursing. I append one of Coleman's diet lists which will furnish this amount of calories in a day (Table 6).

Of course it is not necessary to determine the quantity of calories accurately, the idea is to get as many into the patient as possible. Simple diarrheas will usually respond to an adjustment of the amount of cream (fat) allowed, sometimes the lactose has also to be reduced. It is well to bear in mind that if a patient has aversion for particular foods when well he will continue to dislike them when ill. Schoffman (1941) thought that the use of large amounts of ripe banana was provocative of good results in a small number of cases in children. Some patients cannot tolerate milk in any form or amount. For such, Garton has devised a diet which, according to Wisart, Johantgen and Clarke is used in the University of Michigan Hospital in the form given in Table 7.

TABLE 7—*TYPHOID DIET WITHOUT MILK*

6:30 A.M.	Cup of hot coffee sugar, 2 drachms (8 Gm.) 2 slices of zwieback or toast butter
8:30 A.M.	One portion of oatmeal or Robinson's prepared barley with 6 buttered crackers, saltines
10:30 A.M.	6 ounces of soup various kinds (180 cc.)
12:30 P.M.	1 medium baked potato mashed and prepared with butter and salt 2 thin slices of buttered toast, hot, and 1 cup of hot weak tea with 2 drachms (8 Gm.) of sugar
2:30 P.M.	2 (teaspoonfuls of pudding bread or tapioca 6 saltines
4:30 P.M.	2 ounces (60 Gm.) of rice, farina or cream of wheat mixed with 1 ounce (30 Gm.) of butter and 4 drachms (16 Gm.) of sugar
6:30 P.M.	3 slices buttered toast
8:30 P.M.	6 ounces (180 cc.) of soup

Care of Mouth and Skin—The tongue and mouth tend to become very foul, and the lips cracked and sore, in typhoid fever. The teeth should be kept well brushed and the mouth washed at sufficient intervals with the N.F. alkaline aromatic solution, it is well to anoint the lips with glycerin and water. A daily cleansing bath with soap and water should be given to be followed by an alcohol rub, areas especially liable to the development of bed sores should have alcohol applied to them several times daily and be kept well powdered in the interim. These things have a double purpose: first, they make for the greater comfort of the patient and serve the ends of

ordinary cleanliness and second, they serve to keep up the morale of the patient, to this latter end he should be encouraged to participate actively in the daily routine procedures as much as is possible consistently with the avoidance of fatigue

Control of Temperature—The new tendency in the therapy of all acute fevers is to look upon the rise in temperature as a physiologic process and to direct no drug treatment toward its reduction, and undoubtedly many lives have been thus saved, but I cannot hold with the extremists who would totally disregard all antipyretic measures. External hydrotherapy seems to me a wholly rational and nondangerous measure, not the Brand bath nor perhaps even any of its modifications, but tepid sponge baths with water and alcohol, two parts to one, when the temperature reaches 102.5° to 103° F, (39.4° C) and a carefully applied cold pack (the patient to be placed on two blankets which are doubled lengthwise of the bed under his body, then quickly enveloped to include the arms in a sheet which has been wrung out of cold water, and thoroughly wrapped round with the blankets which are brought up from each side and overlapped) when the temperature becomes excessively high. We were formerly allowed to believe that this shock with the warm glow which subsequently spreads over the body, acts as a tonic to the circulatory apparatus now there are those who cavil even at this but for my own part I still believe that these packs are 'stimulant'

Fluids, Chlorides and Vitamins—Since the patient has fever and is losing a considerable amount of water and salt in consequence, fluids should be given liberally and salt added in considerable quantity to the food or given in the form of the commercial tablets. Most patients will take lemon or orangeade when they rebel at plain water. When the patient's interest cannot be sufficiently aroused to ensure the taking of fluids by mouth resort should be had to hypodermoclysis or proctoclysis with physiologic saline solution. If an adequate diet is not being taken, of course it will become necessary if this state persists very long to begin administration of vitamins in concentrated form.

Care of the Bowels—If the patient is seen early, i.e. before there is any likelihood of intestinal ulceration having already occurred, there is no reason why a dose of 2 or 3 grains (0.13 or 0.2 Gm) of calomel should not be given, followed in a few hours by one of the milder salines such as a Seidlitz powder but I believe that most students of the disease are nowadays opposed to all dosing with cathartics after this time. Typhoid fever most certainly cannot be 'flushed out of the system' and it would therefore seem with the ever present danger of perforation that we are well advised to leave the peristalsis stimulators out of the picture altogether. On the full diet treatment a small soap-suds, or better still physiologic saline enema at a regular time each morning accomplishes the daily evacuation of the rectum and what more is needed? Many men have relinquished the old favorite castor oil but use instead cascara sagrada frequently throughout the course of the disease however even this mild emodin cathartic may at times violently stimulate peristalsis. Liquid petrolatum has enjoyed some vogue of late but I wonder if we will not conclude in time that whatever good may accrue from the employment of this intestinal lubricant is more than counterbalanced by the increased dissemination of the bacilli incident upon the constant leakage of the oil from the rectum.

Diarrhea.—On the full feeding regimen diarrhea is seldom a prominent symptom and when it does occur usually yields to a careful readjustment in the cream and lactose portions of the diet; when it persists, resort is usually had to the tannins or to bismuth. Acetyltannic acid (tannigen) may be given in a dose of 3 to 10 grains (0.2–0.6 Gm.), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids. Protan is given in 5-grain (0.3 Gm.) tablets, from 2 to 6 of which may be given at intervals of two hours or more. Albumin tannate (albutannin or tannalhin) must be given in doses of 30 grains (2 Gm.) or more, in capsules or as a powder. For the employment of bismuth the following is a satisfactory prescription:

R̄ Bismuth subcarbonate	℥j	30 0
Glycerin	℥ss	15 0
Syrup of ginger to make	℥iv	120 0
Label: 1 teaspoonful every two hours for 10 doses		

It is well to avoid the use of opiates in typhoid if possible for the reason that meteorism is likely to follow their withdrawal.

Tympanites.—When this symptom does not yield to dietary adjustment it should be treated as described in the discussion of pneumonia, though of course resort must never be had to pituitrin as there mentioned.

Delirium.—Dissuasion is the best sedative in the treatment of typhoid delirium, but it must be painstakingly and tirelessly employed. When resort to drugs becomes necessary, one of the barbiturates may be used (see list under Insomnia). The following is also a useful sedative prescription, which is not to be used carelessly however:

R̄ Sodium bromide	℥vi	28 0
Chloral hydrate	℥vi	28 0
Peppermint water to make	℥iv	120 0
Label: 1 teaspoonful in water every three or four hours		

In rare cases nowadays is it necessary to apply a restraining sheet, though its more frequent use in the muttering, restless, but not actively delirious state of severe cases would doubtless save much of the patient's strength.

Circulation.—The studies of Brow (1929), and Porter and Bloom (1935), indicate that the serious cardiovascular complications of the old classical form of typhoid fever are no longer seen in these days of adequate feeding. When there is occasional need for a drug, however, coramine or metrazol are probably the drugs of choice. One should perhaps note, too, that many men still prefer $\frac{1}{2}$ to 1 ounce (15–30 cc.) of whiskey, three or more times daily, for "stimulation" in typhoid fever.

Exsanguination-transfusion.—Lantin and Guerrero (1936) withdrew 150 cc. of blood from the patient and then immediately transfused 200 cc. of blood from a donor, repeating the procedure at daily intervals as long as seemed indicated. In their 41 patients so treated the mortality was just about half that in the 34 controls.

Immunotransfusion.—Hahel and Crocker (1936) had the opportunity of using this method of treatment (details in article on Sepsis) in a small number of cases and felt that the results merited its further trial.

Convalescent Serum.—Lantin *et al.* (1939), in the Philippines where plenty of typhoid convalescents are always available, have used 20 cc. of convalescent serum, intravenously or intramuscularly, in 17 cases. They felt that both the course and the fatality rate were favorably influenced by the measure.

Vaccines and Serums.—Just when one had concluded that the use of specific vaccines and serums had been completely abandoned on the basis of their nonefficacy, a serum method has been revived in England. The reports (see Felix, 1935-1936; McSweeney, 1935; Cookson and Facey, 1937; Robertson and Yu, 1936; Schwartzman *et al.*, 1936; McSweeney, 1937, in Bibliography) do not indicate, however, that the practical value of this therapy has been established as yet. Vaccines were also abandoned some years ago because their use frequently increased the severity of the toxic symptoms and seemed to promote intestinal bleeding, but recently they too have been revived in the form of the lysed vaccines prepared as described by Caronia; experience with this vaccine is still too scant to warrant description here.

Sulfonamides.—Harris *et al.* (1930) felt that prontosil and sulfapyridine were beneficial in their 7 cases; De Salvo (1940) failed to affect his case with sulfanilamide and neoprontosil; Wedhaecker *et al.* (1940) thought the thiazole derivatives were of value in 3 of their 4 cases. In short, no study from which one can adequately adjudge these drugs in typhoid has yet appeared.

Hemorrhage.—Keep the patient absolutely quiet by the use of morphine sulfate, $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.008-0.015 Gm.), or dilaudid, $\frac{1}{12}$ grain (0.002 Gm.), every three or four hours; this will also splint the bowel. Withhold all food, and nearly all water, until the bleeding has apparently stopped. Apply continuous cold to the abdomen. Hemostatics are of no value.

Perforation.—Surgical intervention as soon as the diagnosis is made—which is easy to write but difficult of accomplishment for the reason that the diagnosis is oftentimes extremely hard to arrive at and very often a surgeon *with the skill here needed* is not at hand.

Tonics.—Iron, arsenic and strychnine are frequently given during convalescence; I wonder how much they are worth? Some such prescription as the following may be used for a short time:

R	Arsenic trioxide	...	gr ss	0.03
	Extract of nux vomica	.	gr v	0.32
	Reduced iron	.	gr xxx	2.00
	Make 20 capsules			
	Label: 1 capsule three times daily after meals			

PROPHYLAXIS

The prevention of typhoid fever groups itself into three subdivisions in addition to those measures in public health sanitation which are so largely responsible for the reduction in the incidence of the disease in recent years: (a) the care of the patient, (b) treatment of the "carrier" and (c) preventive inoculation.

Care of the Patient.—Everything and everybody coming in contact with the typhoid patient should be considered potentially contaminated. Of course subsequent sterilization of all these objects and persons is a practical impossibility, but it may be approximated by maintaining a state of the

most absolute cleanliness in the room or ward, by screening out and exterminating flies, by insisting that the attendants frequently change their clothing and wash and disinfect their hands, and by frequently changing the patient's clothing and bed linen. All clothing and bed linen are to be boiled thoroughly after each use. The patient is to have individual dishes which are to be boiled after each use. It is doubtful to what extent thorough disinfection of the feces and urinae is accomplished but any one of the following substances should be added to, and thoroughly mixed with the contents of the bed pan and urinal before it is emptied into the toilet or privy: chloride of lime solution ($\frac{1}{2}$ pound to the gallon of water will make a satisfactory solution provided the lime contains enough chlorine to irritate the eyes markedly when brought near the face, otherwise much more must be used); 5 per cent phenol solution, 5 per cent compound cresol solution, 5 per cent solution of sodium hypochlorite (antiformin). The odor and irritating properties of formaldehyde are too great to make its use practicable. When the urinal and bed pan are not in use one of these solutions or a 1:1000 solution of bichloride of mercury, should be allowed to stand in it, in some hospitals it is possible to sterilize these articles completely with live steam, a thing not possible of course in the home.

Treatment of the "Carrier"—The vast strides taken in recent decades in the prevention of typhoid fever through measures of public health control have again brought the typhoid carrier to the forefront in many regions where contaminated water or milk supplies or other unsanitary conditions have practically ceased to exist as channels of dissemination of the disease. Of course the decline in incidence of typhoid has inevitably reduced the number of carriers, and as this declining number of carriers is itself reduced through death from intercurrent disease, the population is tending to sterilize itself by a combination of the several processes. So the carrier problem though now probably one of greater importance in specific instances than ever before because of the fact that these reservoirs of infection remain the only sources of contamination in many areas is upon the whole a problem of declining magnitude. The recent highly interesting studies of Anderson (1936) and his associates of the Massachusetts Department of Health suggest that contrary to previous belief the more recently a carrier has become such the greater menace he is in general, i.e. the carrier of many years' standing has so infected or immunized the immediate environment that new cases will not develop until fresh susceptible material is introduced or until such a carrier in later life is obliged to go roaming and is placed in dangerous juxtaposition, as through a food handling position, to a fresh population.

Lembcke (1939) reported a failure to affect the carrier state by the use of sulfamidamide in 1 case as did Saphir and Howell (1940) also the experience of Levi and Willen (1941) with sulfaguanidine in 1 case indicated only that this drug deserves further trial for it was not apparent that the success they achieved with it was not attributable to the cholecystectomy which had been performed earlier. Onodera *et al.* (1931) suggested the use of soluble iodophthalein as used intravenously for gallbladder visualization and freed 3 of their 7 patients from bacilli after one or two treatments, Saphir and Howell (1940) gave the drug in a dose of 1 drachm (4 Gm.) orally three times during the course of six days with success in their 1 case, Earright (1941) apparently succeeded also with this oral method in his case, but Levi and

Willen (1941) failed in their case though the patient was kept on the regimen for a month.

Cholecystectomy, for the removal of 'nests' of bacilli in the gallbladder, is apparently coming into some favor again. Vogelsong and Haaland (1931) reported 10 cures in 25 operated cases, Seuftner and Coughlin (1933), 35 in 53 cases (there were 8 deaths in the series), Swenson (1933), 9 in 13 cases (3 deaths), Bigelow and Anderson (1933), 12 in 12 cases, Collier *et al* (1937) 16 in 18 cases, Hanssen (1939), 7 in 8 cases.

Of one fact we have no doubt: the detected carrier must be trained in personal hygiene and prevented from engaging in food handling occupations—measures which, if they can be enforced, are probably sufficient in themselves to protect the family and community.

Preventive Inoculation—World War I conclusively proved the worth of prophylactic vaccination against typhoid and paratyphoid fevers, and experience in civilian life all over the world (for example, in the C C C camps, as reported by Lull, 1936) since that war, together with that accumulating in World War II, has continued to add to the favorable evidence.

The vaccines in use today vary somewhat in the details of their preparation and content but any of them which meets the standard requirements of USP XI is acceptable. For a time the monovalent vaccine, *v c*, containing killed typhoid organisms but no paratyphoids, was preferred because it was felt that paratyphoid fever incidence was very low and the omission of these organisms markedly decreased the number of systemic reactions to vaccination. However, paratyphoid cases did occur during this period and the swing has now set in back toward the triple vaccine containing the typhoid and the two paratyphoid organisms. It is this triple vaccine which is being used in our Army at present. The studies of Grasset (1939) with an endotoxoid vaccine and of Tuft (1940) with an intracutaneous method of administering ordinary vaccine are very interesting and worthy of closest scrutiny regarding effectiveness for the claim is made for both that the incidence and severity of reactions are much reduced. Attempts to confer protective passive immunization of a temporary nature by use of the Felix antiserum, previously referred to, are still entirely in the experimental stage and will likely at best not have a great deal to offer under ordinary circumstances. For many years the method of immunization by the oral route as advocated by Besredka has been on trial in various parts of the world, but in spite of the vast amount of literature which has appeared in support of this method, the medical corps of none of the world's present great armies (so far as I am aware) has been convinced to the point of substituting the oral for the injection method despite the admitted ease of administration and freedom from reactions of the latter. The oral route having had so long a trial and still being without a secure place should afford sufficient evidence to warrant the general practitioner to adhere yet awhile to the injection technique.

The injections are made subcutaneously (*not* intramuscularly) in the deltoid region at intervals of about a week. There is nearly always a local reaction of some severity, if, for any reason, the abdomen has been chosen for the injections, a more painful reaction must be expected even than that which occurs in the arm, and the reaction in the thigh is so severe as practically to contraindicate the use of this site. The general reaction which follows in six to ten hours after the injection, is characterized by chills and

fever, backache, headache, muscular pains, and in some cases nausea and vomiting and even diarrhea. Most individuals experience some degree of this reaction after one or more (usually the middle) injections, but it usually lasts not more than twenty four hours and can be minimized by remaining inactive after the injection.

After the fifth month of pregnancy women are usually not vaccinated, nor are menstruating women, nor infants under two years. Lopez Rizal Arguelles and Lara, in Manila, have shown that nursing infants are immunized by vaccinating the mother. Regarding other contraindications Russel writes "No one with a temperature above normal should be vaccinated until the temperature has fallen and a normal state of health has been restored. Endocarditis, and particularly nephritis, are contraindications. Clovis and Mills, and Brown, Heise, Petroff, and Wilson have shown that patients with inactive tuberculosis may have typhoid fever, or antityphoid vaccination, without any detrimental effects on the pulmonary condition, and that patients with active tuberculosis may have typhoid fever or antityphoid immunization without a more rapid advance in their pulmonary condition than they would have had otherwise. The first authors also note that the pulmonary tuberculosis did not have any appreciable effect on the course of the typhoid fever."

The adult dose is 0.5 cc for the first injection and 1 cc for each of the two subsequent injections. I find three "rules" for dosage in children above two years: (a) Adjust the dose accordingly as the weight varies from that of the average adult, taken to be 150 pounds. (b) One twentieth of adult dose between two and four, and $\frac{1}{2}$ between four and twelve years (Brit. Med. Assoc. Special Committee Report June 22, 1935). (c) Children over eight years, full adult dose, under eight years, $\frac{2}{3}$ adult dose (Sanford 1936). As a rule children experience no reactions or only mild ones.

Maximum protection is certainly had within two or at most three months but there is apparently some response within a few days, as indicated by study of the agglutinin titer of the serum. From time to time doubt has been expressed of the advisability of vaccinating in the presence of an epidemic because of the alleged 'negative phase' resulting from the inoculation but the only controlled clinical experiment on this point of which I am aware—the study of Ramsey, in 1935—showed that certainly after completion of the three injections, 1 cc after two weeks but doubtfully after only one or two injections, 1 cc, after only one week, the case incidence was significantly reduced. Schutze's (1939) animal experimentation certainly yielded evidence in support of vaccination during an epidemic. For the allegation that cases developing in spite of vaccination are milder than they would otherwise have been, I know of no real support from controlled observation.

It is not yet definitely known how long immunity lasts after typhoid vaccination. Longfellow and Luippold's (1940) mouse protection tests indicated that revaccination of the human with a single dose of 0.1 cc of vaccine intracutaneously (relative freedom from reactions), or 0.5 cc subcutaneously, reliably renews immunity and that such revaccination should preferably take place each year and certainly at not longer than two-year intervals. Apparently, however, the Army practice (Col. Simmons, 1941) will be to revaccinate at the end of three years except for individuals over forty-five years of age.

VINCENT'S ANGINA

(Fusospirillosis, Trench Mouth)

This is an acute infectious disease which seems to have been endemic throughout the world for a long time but was not forcibly brought to the attention of more than a few physicians and dentists until it became epidemic in the armies during the first World War since which time it has been recognized with increasing frequency among the civilian populations of all countries. It is primarily an affection of the tonsillar area and pharynx the floor of the mouth the gums about the teeth and more rarely of the tongue lips and cheeks. The mouth lesions are single or multiple small red areas which become gray sloughing patches and finally ulcerate and are covered with a yellowish gray pseudomembrane the latter is easily removed and displays a bleeding surface beneath, but it soon becomes covered over again. The breath has nearly always a fetid odor and the interference with eating may be great due to the pain of chewing and swallowing and there is often an adenitis but only in exceptional cases are there very marked constitutional symptoms in adults. Note should be taken however, of Goldman and Kully's (1933) report of 7 fatal cases in the Cincinnati General Hospital from 1929 through the first six months of 1932, in 6 of the cases there was very extensive ulceration which likely offered a portal of entry for other organisms in the seventh case edema and sepsis played prominent roles. Black (1938) presents the malady in young children as an acute febrile affair with considerable constitutional reaction but a benign and self limited course.

Pulmonary complications often confused with pulmonary tuberculosis are being recognized with increasing frequency, they may take the form of pulmonary gangrene or abscess, ulceration of the bronchi, lobar pneumonia bronchopneumonia, or empyema, apparently the disease may also appear primarily in the lungs. Infection of mucous membranes other than those of the respiratory passages and recovery of the organisms from the parathyroid organs has been reported numerous times. Both a spirillum and a fusiform bacillus are easily found in stained smears from the lesions. Whether these are pleomorphic forms of a single organism or whether they are really two distinct organisms living in symbiosis is still a moot point, indeed the fusiform bacillus at least is more than likely a normal inhabitant of the healthy mouth and some observers doubt the causative role of either the bacillus or the spirillum in the disease.

In every case of suspected Vincent's angina blood study should be performed to make sure that the patient is not really suffering from agranulocytosis.

If any carefully controlled studies of therapy in Vincent's infection have ever been performed I am unaware of it, which explains the multiplicity of agents necessarily mentioned below.

Hydrogen Peroxide—Farrell and McNichols (1937), in a review of their 704 cases, stated that hydrogen peroxide is the most important agent in treatment all other substances being only adjuvant. They used it in all cases, four or more times daily, full strength. Many men agree that the drug is good but do not employ such heroic therapy, preferring to dilute the agent with at least one part of water. Field (1940) dilutes with one part of hot water but

says that care must be taken not to produce chemical burns with this solution.

Zinc Peroxide.—Meleney (1938) and a number of others prefer this agent, making a paste of the powder for local application and using 1 part drug to 4 parts water for a mouth wash.

Sodium Perborate.—This agent was extensively employed during World War I and later popularized in the United States by Bloodgood at Johns Hopkins Hospital. A thick paste was made with water and smeared over the teeth and the lesions with the fingers. After five minutes the mouth was rinsed out with water. In some instances a dilute solution was used as a gargle. Fantus (1935) offered the following prescription for an aromatic preparation of the perborate:

R) Glucose (saccharine)	gr ½	0 01
Oil of peppermint	mgx	0 60
Sodium perborate . . .	3i	30 00
Label: Teaspoonful or two in tumblerful of warm water as mouth wash or gargle		

Not many men were able to obtain the results Bloodgood so enthusiastically claimed, but many did see a considerable number of chemical burns with the perborate and it was finally realized also that the substance is very unstable and that lots of it vary greatly in strength. This drug is therefore not nearly so popular now as formerly.

Arsphenamine, Neoarsphenamine, or Mapharsen Locally.—Many men use one of the preceding oxidizing agents as a mouth wash and then after rinsing the mouth dip a moistened cotton applicator into one of the above arsenicals and rub the particles into the lesions, or else they apply the drug in 10 per cent solution in glucose or glycerin. I quote Barker on the method of getting the powder between the teeth:

"The application of arsphenamine in these spaces is accomplished with facility by taking pieces of coarse knitting wool about 2 inches long, moistening them with water, and dipping them in the powdered salvarsan. These bits of yarn are threaded between the teeth and sawed back and forth after the manner of dental floss, and are then allowed to remain in place for from fifteen minutes to half an hour."

The entire treatment, consisting of the cleansing with an oxidizing agent, the washing out of the oxidizing agent, and the rubbing in of the arsenical, should be employed two or three times daily in severe cases. No harm will be done if small amounts of these arsenical preparations are swallowed.

Arsenicals Parenterally.—These drugs are usually given in smaller doses than are employed in the treatment of syphilis. It should be noted that Vincent's angina has been known to appear and become quite severe in persons who were at the time undergoing routine intravenous arsenical treatment for syphilis.

In the pulmonary cases, any of the organic arsenicals are used as in the treatment of syphilis. Excellent results have been reported by Kline and Berger, 1925; Smith, 1930; Heffernan, 1932; Spector, 1933—but Field (1940) seems to doubt these results and says that he could not confirm them in his own cases, the number of which is not stated. Maxwell (1936) has reported good results with acetarsone (stovarsol) given by mouth. Black

(1938) says that parenterally administered sulfarsphenamine is not effective in these infections in children and should not be used. Kolmer (1930) found that bismarsen was helpful in 6 cases of the oral type which seemed unusually severe.

Nicotinic Acid—Because of the presence of large numbers of fusiform bacilli in pellagrous stomatitis, King (1940) has administered nicotinic acid with excellent results in 34 cases. He gave from 60 to 250 mg. of the drug daily by mouth.

Ascorbic Acid (Vitamin C)—Because of existing experimental evidence that low ascorbic acid levels might be associated with infections of this type, Field (1940) suggests that in critical situations 2.5 Gm. of this substance be administered intravenously in doses of 0.5 Gm. spread out through twenty-four to thirty-six hours, large amounts of the vitamin from natural sources such as oranges and lemons should also be given.

Bismuth and Antimony—There are reports of the successful use of both these agents, the former as in syphilis, the latter as in kala-azar or in bilharziasis (see Index for all these diseases).

Bowman's Solution—This is a mixture of wine of ipecac, $\frac{1}{2}$ ounce (15 cc.), glycerin, 1 drachm (4 cc.), and solution of potassium arsenite to make 1 ounce (32 cc.). In mild cases this preparation seems to effect a cure if a few drops are used on a soft toothbrush with thorough scrubbing several times a day, and in more severe cases it is good adjunct treatment. One has to be a bit careful with it, however, for some of the potassium arsenite solution (Fowler's solution) may be swallowed, or it is conceivable that quite large amounts of it might be absorbed through eroded surfaces.

Miscellaneous Agents for Local Application—Practically all the antiseptics and disinfectants have at one time or another been advocated for local use in this disease. Those which have had the greatest vogue are tincture of iodine, 5 to 10 per cent chromic acid, 10 per cent silver nitrate, 2 per cent zinc chloride, 1 per cent potassium permanganate, 2 per cent methylene blue, 1 per cent acriflavine (trypanflavine), hexylresorcinol (ST-37) solution, and potassium chlorate in saturated solution. The results obtained with these substances do not warrant special mention here. The careful studies of Reasoner and Gill (1927) showed that solutions of ordinary toilet soaps, as well as pure soaps prepared in the laboratory, have a definite spirocheticidal effect, and that their use in dentifrices assists in keeping the oral cavity free from mouth spirochetes, thereby affording a measure of protection against tissue infection with the Vincent organisms.

WHOOPIING COUGH

(*Pertussis*)

Whooping cough is an acute infectious disease which we now believe is probably caused by *Haemophilus pertussis*. It is highly communicable and is therefore principally seen in very young children, nearly 50 per cent of cases are in infants under two years of age. There is no distinctive gross or microscopic pathology and the disease is therefore looked upon as one which

remains local throughout its course. One attack is almost universally considered to confer life long immunity, most observers looking upon the exceedingly rare second infections as really first infections in individuals who did not truly have whooping cough the "first" time. There are apparently a great many persons who possess a natural immunity to the disease.

There is an incubation period of three to twenty days and then another week or two during which the symptoms are those of coryza and bronchitis with cough. Gradually during the latter part of this period the paroxysmal nature of this cough becomes apparent and clinical diagnosis is then possible. The paroxysmal stage is characterized by a very distinctive group of symptoms: the patient usually clutches at something for support and then begins a series of rapid, short, loud coughs, during which the tongue is protruded from the mouth, the eyes water and become injected, and the face is suffused or deeply cyanotic, and at the end of which there is a deep inspiration through the narrowed glottis, which causes the "whooping" sound (paroxysmal sneezing in rare instances may apparently replace coughing). In most cases there are several such attacks in quick succession, but they cease at once for the time being when a little mass of glairy mucus is brought up. There is often vomiting during the seizure and many times bleeding from the nose and other mucous membranes. The subconjunctival hemorrhages which occur are usually ascribed to the violence of the coughing. Altogether the attacks are a distressing thing to witness as well as to experience. Between paroxysms the patients, if old enough, are sufficiently undisturbed to engage in their customary amount of activity provided the case is of average severity. The "whooping" period usually lasts from three to six weeks but in many cases it is protracted for a much longer period, it subsides finally into a subacute bronchitis which often persists for many months. Sauer (1937) has said that there is an annual average of 200,000 reported cases of whooping cough in the United States, with 5200 deaths, or 1 death for every 39 cases reported. In young children, and especially those debilitated by any other cause, the fatality rate may be as high as 60 per cent. Bronchopneumonia is the complication that accounts for most of the deaths. Cardiac complications are rare, but Nelson's (1939) thorough review indicates that neurological complications occur perhaps more frequently than has been thought. Meningeal or other hemorrhage due to violent coughing is a rare complication in children but one that is very dire in its results, of course it is the greater likelihood of such an occurrence in adults which makes us always apprehensive upon diagnosing whooping cough in one of advanced years. Surprisingly, whooping cough does not seem to be as harmful in active tuberculosis as one would think it should be.

The disease is transmissible throughout the prodromal period and up to and including the first part—but just how much of the first part, is not known—of the whooping period. Many departments of health in the United States require that the child be kept out of school until he no longer whoops but elsewhere, notably in France and Denmark, he is permitted to return after he has been whooping for four weeks, in England (Smith, 1936), it seems that the period recommended is six weeks. The finding of the organism by the "cough plate" method is considered a valuable aid in establishing diagnosis before the whoop appears. During and after the second week there is nearly always a relative and absolute lymphocytosis.

Whooping cough was apparently unknown to the ancients nor is it mentioned by physicians of the Middle Ages De Baillou described the first epidemic in Paris in 1578 By the middle of the eighteenth century it was widespread throughout the civilized world It reached the Western Hemisphere in 1732, but for some strange reason Australia escaped until 1890 The disease is very mild in the tropics

THERAPY

There are two measures of paramount importance in the treatment of whooping cough First, the child should be kept out of doors as much as possible, for in this way far better than any other will the number of paroxysms be reduced While not denying the influence of fresh air in bringing about this effect, I am inclined to believe that a more important factor is the child's immersion of himself in enjoyable play Who has not seen a little tot trudging a weary circuit of the park hand in hand with a bored nurse, who had to assist him through a cough and vomit at short intervals while a group of nearby children, kept out of school by the same disease, were merrily romping past some of their attacks? Confinement within doors, or attachment to the apron strings without doors, is an irksome thing to the normal robust child, irksomeness makes for irritability, and irritability undoubtedly increases the number of paroxysms in whooping cough Of course we cannot put very young or very puny children out of doors, so for them the best we can do is to provide adequate ventilation of the house and change them about from room to room for diversion

The second matter of great importance is the feeding of the patient, for the frequent vomiting in severe cases often brings about a state of malnutrition almost before we realize it To treat of this phase of the subject adequately would carry me into the field of infant feeding where I certainly am not qualified to go, nor would such an excursion be fairly within the scope of this book Suffice it to say, therefore, that a radical reduction in the amount of fluids and the replacing of the regular feeding periods by a number of small feedings at short intervals between the paroxysms, is usually provocative of good results in children of all ages

Of drugs and biologicals I must necessarily have much to say because *the subject cannot be summarily dismissed*, but I would wish to preface what follows with a tripart statement (1) There is as yet in whooping cough no remedial agent that even approaches specific value (2) Other things being equal, turning the child free out of doors in mild cases, and carefully nursing him, i. e., providing comfort and nutrition and diversion and sharply watching for complications and emergencies in severe cases, are the simple mandates in the handling of the disease (3) The fewer drugs placed in the stomach the better

Sedatives—In mild cases, especially when the weather and other conditions make it possible to turn the patient out of doors, the use of drugs of this class is usually unnecessary, though the night will often be very disturbed unless a sedative is given at bedtime A teaspoonful of the following mixture (4 grains each of the chloral hydrate and sodium bromide) may be given to a child of five or six if he is robust and of the average weight

R Chloral hydrate	℥j	4 0
Sodium bromide	℥j	4 0
Syrup of orange to make	℥ij	60 0

Or, since belladonna seems to be of some value here (see below), the bromide may be combined with a member of that group, ns in the following

Sodium bromide	℥j	4 0
Tincture of hyoscyamus	℥j	4 0
Tincture sweet orange peel to make	℥ij	60 0

Epstein (1938) has been very much pleased with the use of gold tri bromide in 330 children. In the beginning of his studies the average dose of $\frac{1}{16}$ to $\frac{1}{8}$ grain (0.003-0.006 Gm) was given in solution three times daily ($\frac{1}{16}$ grain, 0.002 Gm, in very young children), but he now prefers to use the "elixir bromaurate," which is a uniform elixir of gold tribromide, the average dosage of the elixir is a teaspoonful every four hours for children, 2 teaspoonfuls for adults. Henricke (1930) used a capsule containing sodium nmytnl, $\frac{1}{2}$ grain (0.03 Gm), and amidopyrine, $3\frac{1}{2}$ grains (0.22 Gm), administering the contents of $\frac{1}{2}$ to 1 such capsule according to age (one to seven years), one half hour before bedtime in jelly, followed by a hot drink or one-half hour before mealtime and at midnight if necessary. I imagine that, in view of amidopyrine's proved potential toxicity (see Agranulocytosis) acetanilid in 2 grain (0.12 Gm) amounts had better be substituted for it in the above. Chlorbutanol (chlorotone) is said also to be useful as a sedative here. Two grains (0.13 Gm) may be dissolved in a little whiskey, sweetened and diluted to taste, and given to a child of five or six. Older children may take it in capsules, the adult dose is 5 to 20 grains (0.32-1.3 Gm).

In severe cases in which it is necessary to make some attempt to control the paroxysms throughout the twenty four hours, antipyrine is much used. Practically all writers are agreed that it is worth a trial in every case. I am not able to explain the effectiveness of this very mild sedative, nor do I know of a careful study of its use with control cases. Regarding administration, Haynes and St. Lawrence write "The former, antipyrine, may be used with safety in doses of 1 grain every three hours to an infant of six months. Later it may be increased to 1 grain every two hours. At two years of age 2 grains may be given at four- to six hour intervals, gradually increasing the frequency until 2 grains every two hours is reached. The drug is well tolerated in fairly large doses by children. Sodium-bromide may be combined with the antipyrine."

Belladonna is also rather universally used. Regarding this drug the same authors write "In using belladonna it is important to begin with small doses and to exercise care in increasing their frequency and size. It is well to begin with $\frac{1}{16}$ of a minim of the fluid extract three times a day for an infant of six months. At two years $\frac{1}{2}$ of a minim may be given every four hours, gradually increasing until it is given every two hours." It is claimed that the antipyrine or the belladonna lessens the frequency but does not reduce the violence of the paroxysms.

Ether in oil by rectum was introduced into the therapeutics of whooping cough a good many years ago by Elgood. It continues to enjoy good repute for the control of severely paroxysmal cases, the most recent favorable

report I have seen being that of Musser (1941), in New Orleans. A 50-50 mixture of ether and olive oil, in a dose of 1 drachm (4 cc) per year of apparent age, is injected into the rectum and the buttocks held together for a few minutes until there is no longer danger of the mixture being expelled.

Ephedrine and Synephrin—Anderson and Homan obtained relief from the spasmodic symptoms in 18 of 20 cases in which ephedrine hydrochloride was used $\frac{1}{4}$ gram (0.015 Gm) to children over one year of age, $\frac{1}{8}$ grain (0.009 Gm) to those younger, in solution at bedtime, or night and morning and occasionally three times daily. Some of the usual toxic symptoms were observed. Synephrin is used in doses of $1\frac{1}{2}$ grains (0.1 Gm), scaled up or down for age, it is said to cause fewer side-effects than ephedrine.

Inhalants—Occasionally a patient is benefited by the use of some such preparation for inhalation as is described in the discussion of the Common Cold. Epstein uses a teaspoonful of his elixir of gold trichloride in this way. However, these inhalants should not be used in children who are running in and out of doors during the colder months, for the mucous membrane seems to be especially susceptible to secondary infection for an hour or more after their use.

Henderson (1932) administered his well known mixture of 6 or 7 per cent carbon dioxide and air (or oxygen) to 10 children nine months to seven years of age, using either the common portable infant inhalator or a specially constructed tent. In all cases the distressing paroxysms of coughing were much relieved in three or four days and the treatment could be stopped by the end of the eighth day.

Abdominal Binder—In 1907, Kilmer reported that general improvement, and especially a reduction in the number of vomiting spells was noted in 95 per cent of 550 cases treated with an elastic abdominal belt. Since that time this device has come to be employed by a great many practitioners usually employing Luttinger's modified binder (marketed by Becton Dickinson and Company). This author says:

"I found these bandages very serviceable in all stages of whooping cough. When applied early, they positively lessen the number of vomiting spells, and thereby contribute to better nourishment and resistance to the infection. The child is comfortable and the older children often cry for it. They seem to feel a sense of security with it as they have 'something to cough against.' I do not think the bandage has any direct influence on the paroxysms. The improvement noticed by Kilmer was probably due to its indirect effect of promoting the general comfort and preventing vomiting. It is possible that this is due to pressure on the vagus as it has been noticed by ocean travelers that tightening the abdomen often prevents seasickness. In view of the decided benefit from the wearing of the abdominal bandage particularly the almost immediate disappearance of the vomiting I strongly recommend its use in every case of pertussis."

Ascorbic Acid (Vitamin C)—Otani (1936), and Ormerod *et al* (1937) found it of advantage to administer ascorbic acid in large doses as in scurvy (q.v.), but Gairdner (1938) failed to confirm them in a controlled series of cases.

Vaccines—Trials of therapy with vaccines of several different sorts have been going on for years, but the evidence is very conflicting and it does not seem to me that any of these methods merits description as yet.

PROPHYLAXIS

Vaccine (Sauer) —In no other disease do the many variables which must be taken into account in estimating the value of prophylactic measures form so great a stumbling block for the investigator, however well intentioned and earnest he may be, as in whooping cough. To date, the only fact we know with certainty is that the older classical forms of pertussis vaccine had no value as preventives of the disease. Whether the newer type vaccine of Sauer (recently isolated strains of *Haemophilus pertussis* are grown on Bordet culture medium containing human blood) will eventually prove as universally satisfactory as a few observers already believe will apparently take a long time in the proving. Of the recent reports which covered a sufficiently large number of injected individuals and controls and were conducted over a long enough period, to give them perhaps as much statistical significance as can be attained in this disease, those favorable to the vaccine as decreasing the incidence in exposed contacts were the Evanston study of Sauer (1939), the San Francisco study of Miller and Faher (1939), the Grand Rapids study of Kendrick and Eldering (1939), the San Francisco study of Singer Brooks (1940), and the Chicago study of Rambar *et al* (1941). Unfavorable findings came from the New York study of Siegel and Goldberger (1937), and the Cleveland study of Doull *et al* (1939). There is mention in practically all reports of attacks of lessened severity in those contracting the disease after injection, I do not know how this point is determined in a disease so absolutely variable as whooping cough.

Sauer now prefers to use the new double strength vaccine which contains 20,000 million organisms per 1 cc. Three subcutaneous injections are given as follows: 1 cc. in the left deltoid region, two weeks later, 1.5 cc. in the right deltoid region, two weeks later, 1.5 cc. in the left triceps region. The best time to begin these injections is when the child reaches the age of six months (see Smallpox for a complete immunization schedule). Mild local reactions may occur and subcutaneous nodules appear which persist for a few weeks but require no treatment. Occasionally there is a loss of appetite and rise of temperature for twenty-four hours but the vaccine contains no foreign serum and therefore does not sensitize the patient to other serum. The point is especially stressed that the vaccine must be stored in a cold refrigerator at all times.

This vaccine has not yet been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Convalescent Blood or Serum and Hyperimmune Serum —Many investigators have tried these measures (description and methods under Measles). Bradford (1935) thought that probably there is some preventive value if the blood is given to contact cases before the catarrhal symptoms develop. Meader (1937) remarks that with an incubation period so long as it is in whooping cough success is likely to be obtained only in those who have fortuitously received the serum soon after exposure, he finds that the most favorable results are had with children in the first three years of life who have been exposed not more than six or seven days. Cohen *et al* (1940) used convalescent serum from donors in the eighth to tenth week of the disease in doses of 5 to 40 cc. intramuscularly, and also hyperimmune serum from donors who had been injected with Sauer's vaccine over a period of six weeks. McGuinness *et al* (1940) also used hyperimmune serum prepared by inject

ing adults who had had whooping cough in childhood with three courses of Sauer's vaccine, each course consisting of three weekly injections of 2, 3 and 3 cc respectively, one month after the last course the serum was obtained and processed by the lyophile method, most of the donors continued to receive courses of vaccine and were bled at one- to two-month intervals. Ten to 20 cc of this serum was injected intramuscularly into children upon exposure. Both the convalescent serum and hyperimmune serum are reported upon favorably by these two groups of workers.

YAWS

(*Frambesia Tropica*, Pilon, Bubas)

Yaws is an infectious disease of the tropics which is acute in its onset but chronic in its course, the early manifestations being most frequently seen in children and young adults. After a noncharacteristic prodromal period of two to four weeks, there appears a skin lesion known as the "mother yaw," usually upon the site of an abrasion on a lower extremity. From one to three months after the appearance of this primary lesion, during which time the patient has generally been free of systemic symptoms, the secondary stage begins. This stage is characterized by a brief period of headache, rheumatic pains and intermittent fever, and then the appearance of the secondary crop of lesions. The eruption is quite generalized but occurs with greatest frequency on the limbs and face, there may be a ring of lesions around the anus and mouth, the scalp nearly always escapes. Characteristically a "yaw" is a nodule varying in size from a pea to a large nut and covered by a yellow or yellowish brown crust from beneath which there exudes a thin fluid. If the crust is removed, there is revealed a raw surface whose fungoid granulations have given the name "frambesia" to the disease (*frambesia* raspberry). Surrounding this lesion there is a dark area in natives, a reddish area in whites. The lymph glands often enlarge in groups but never become painful or suppurate. Mucous membrane lesions are very rare, perhaps they do not occur at all, but the mucocutaneous junctions are frequently involved. Occasionally there is a juxta articular condition closely resembling acute rheumatic fever, but it does not respond to the salicylates. The lesions which are usually itchy but never painful, disappear in three to six months in children and six to twelve months in adults, leaving behind pigmented or hyperpigmented areas. Most cases terminate at this point, but when a tertiary stage appears it is characterized by a periostitis or osteitis, or by a gummatous type of nodule or ulceration, which on healing accounts for much later deformity, it is impossible to make clinical differentiation between these lesions and those of tertiary syphilis (Pardo-Castello, 1939, Fox 1939). Gangosa, a very destructive condition of the nose and mouth, which often before it subsides has converted the two cavities into one hideous opening in an almost featureless face, is most probably an unusual manifestation of third stage yaws.

The causative organism, *Treponema pertenue* (Castellani, 1905), may be found in abundance within the thickened epidermis in early yaws and also

as shown by Goodpasture, within the perivascular connective tissue of the papillae. This organism can be differentiated with difficulty if at all from *T. pallidum* of syphilis, but the lesions which appear when it is inoculated experimentally in both animals and man differ clinically and histopathologically from those of the latter disease. In addition, the primary lesion is never venereal, the central nervous system is not attacked and the cardiovascular system probably not (Weller's studies on this latter point, though still inconclusive, are very interesting, however), the disease is not congenitally acquired, and an individual may have both yaws and syphilis at the same time. The Wassermann and Kahn tests are positive in yaws as in syphilis.

Castellani opines that the disease may have had its original home in Africa since epidemics frequently broke out on slave ships and the early planters in the West Indies quarantined the newly arrived slaves in an attempt to hold it in check. At the present time it does not occur indigenously in Europe, the United States, or Canada, and imported cases do not effect a spread in these lands. But it abounds in tropical Africa and Madagascar, in southern Formosa, in the Federated Malay States in French Indo China and in the Netherlands Indies. It is common in southern China and in Burma, Assam and Ceylon, but is rare in India proper, particularly in the western part. It is very prevalent in the West Indies, some parts of Central America and the northern parts of South America, in the Philippines in Australia and New Guinea, and in all the mid Pacific islands. The studies of Ramsey among the hill tribes of Assam, and of Lopez Rizal and Sellards in the mountains of northern Luzon, have completely upset the previous belief that the disease is confined exclusively to lowlands, though in the highlands it does assume a somewhat different character.

To the historically inclined student, the controversy regarding the alleged identity of yaws and syphilis is of immense concern, but lack of space together with that declining temerity which paces the marching years, forbid me to enter into the matter here. The especially interested reader will find that the published studies of Rear Admiral Butler (MC) USN, and of Captain Holcomb of the same Service, and those of Professor Blacklock of the School of Tropical Medicine in Liverpool, England, and the interesting treatise of Hamlin (1939), will lead him into the voluminous literature. As one entirely outside the subject I cannot refrain from remarking, however, that the demonstration by Kumm and Turner (1936), of the Jamaica Yaws Commission, of the transmission of yaws from man to rabbits by an insect vector of the *Hippelates* genus, seems the most important contribution to the subject in recent times, and that should it prove possible to show that transmission commonly occurs in this way between man and man in nature, a truly epochal reorientation will have been effected in the study of the disease.

THERAPY

Neocarsphenamine—It is often stated, and I suppose quite generally believed by nonworkers in yaws, that one intravenous injection of this drug suffices to cure any case of the disease. This belief, however, accords but very poorly with the actual facts as they were developed by the excellent studies of Moss and his associates in Santo Domingo some years ago. These workers

treated 1046 cases. About one half of the patients were reexamined from one to six weeks after treatment of 362 patients given a single injection, only 19.8 per cent were cured or practically cured at this time, while of 169 given 2 injections, 51.5 per cent were cured or practically cured. The final conclusion, however, based upon another examination of 419 of the original 1046 patients, which was made nearly five years after their treatment, indicated that about 50 per cent of a miscellaneous series of yaws cases may be cured by one injection, that a second injection does not greatly raise this percentage, but that three injections very considerably increase the number of permanent clinical cures. More recent observations of others indicate that even much more prolonged treatment than this does not reduce the Wassermann reaction in more than half the cases treated intensively for three years (Gotay *et al.*, 1935). During a brief visit to Haiti, some years ago, I gained the definite impression that the one injection treatment is not looked upon as satisfactory there, but that it is recognized as a necessary compromise with the ideal since most patients are so much improved by the injection that, unless hospitalized, they do not return for subsequent treatment. Castellani writes: "Three to six injections at three- to six-day intervals are generally sufficient to obtain a clinical cure, though in many cases one injection is sufficient to make all the symptoms disappear." But Pardo Castello (1939) says that the number and frequency of relapses and the persistently positive serological reactions incline him to say that yaws is as difficult to cure as syphilis, and that the treatment should be, as for syphilis, early, vigorous and continuous. As in syphilis, one injection causes the disappearance of the organism from early lesions within forty hours (Goodpasture, 1928).

Directions for the preparation and injection, and precautions with regard to the use, of neoarsphenamine appear in the article on early syphilis.

Mapharsen—I have seen no mention as yet of the use of this drug but it will surely be very popular eventually because of its relative freedom from reactive properties.

Acetarson (Stovarsol)—Pardo Castello (1939) obtained satisfactory clinical results with this drug but of course no more effect on the serological reactions than with neoarsphenamine. He finds it useful in native populations not only because it can be taken by mouth but because it is inexpensive. His course consisted of 4 grains (0.25 Gm.) daily for twenty days, 3 to 6 such courses being given with rest periods of two weeks between.

Bismuth—The various preparations of this drug suitable for intramuscular injection, the precautions, reactions, etc., are discussed in the article on early syphilis. Where insuperable obstacles to the use of arsenicals are encountered, bismuth may be employed instead, but Turner and Saunders (1933), of the Jamaica Yaws Commission, doubtless express the consensus when they say "the relapse rate for patients treated with bismuth salicylate is enormously higher than for those treated with neoarsphenamine." The use of the two drugs in supplementary fashion as in syphilis is the ideal which at present there seems little hope of attaining in most of the "native" portions of the globe. In his most recent report, Saunders (1937) states that the difference between the effects obtained with neoarsphenamine and with bismuth is not great enough to offset the greater ease of administration and lower cost of the latter drug. He and his associates have found that under field conditions, 4, but preferably 6, weekly injections are the ideal.

Tartar Emetic and Potassium Iodide—These two drugs are usually employed in the following formula, which is known everywhere in the tropics especially of the eastern hemisphere, as "**Castellani's Yaws Mixture**"

Tartar emetic	gr j	0 085
Potassium iodide	ʒj	4 000
Sodium salicylate	gr x	0 650
Sodium bicarbonate	gr xv	1 000
Water (or chloroform water) to make	ʒj	32 000

This amount (1 ounce of the mixture), diluted to three or four times the volume with water, is given three times daily to adults, counting every one over fourteen years an adult, half doses are given to children of eight to fourteen, and one third or less to younger children. Only the tartar emetic and potassium iodide are active against the causative organism, sodium salicylate being added to hasten the disappearance of the thick crusts and sodium bicarbonate in the hope of lessening the emetic properties of the mixture. *This latter drug renders the preparation cloudy and inelegant, though it becomes clear when diluted with water at the time of administration.* If emesis is produced, Castellani advises that the sodium bicarbonate be increased or that a small amount of an opiate be given before each dose. Europeans do not stand the full doses so well as do natives.

The mixture is given for ten to fifteen days, discontinued for a week and then given again for ten to fifteen days. The use of this formula is said to give very good results though neoarsphenamine is preferred wherever it can be obtained.

YELLOW FEVER

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis, and yellow fever, and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

FLUKE INFESTATION

I LUKE INTESTATION

INTESTINAL FLUKES

Throughout a wide territory in the Far East, in the Japanese archipelago, the Philippines, and in a few other scattered areas man is infested by a rather large number of intestinal flukes, but the only one of these of sufficient importance to warrant discussion in such a book as this is *Fasciolopsis buski* which gives rise to a syndrome of diarrhea, anemia and edema in a very small proportion of the individuals who harbor it. Those who have studied the disease are agreed that death, when it occurs is apparently due to exhaustion. The vicious circle responsible for the perpetuation of the malady is as follows: (a) the use of human excrement containing eggs for fertilizer, (b) the hatching of the eggs in the water and their penetration into the body of certain snails wherein they pass a portion of their life cycle, (c) eruption of metamorphosed forms from the snail and their encystment on aquatic plants, (d) the eating raw, of contaminated water nuts (e) maturation of the fluke in the human intestine where it sows its eggs.

THERAPY

Under proper anthelmintic treatment dead flukes appear in the stools within twelve hours. Thymol, betanaphthol, carbon tetrachloride and hexyl resorcinol have all been used successfully (for details of their employment see the section on Worms). Barlow (1925) favored carbon tetrachloride, but a more recent report on a large number of treated cases is that of McCoy and Chiu (1937), who used hexylresorcinol. Faust (1939) thinks that possibly tetrachlorethylene will prove satisfactory.

LIVER FLUKES

Liver flukes are common parasites in sheep, cattle, pigs, dogs and cats. The human cases have about the same geographic distribution as that of the intestinal flukes (see above). Of the several encountered in man, *Clonorchis sinensis* is the most important (though current investigators among whom Bacigalupo [1938] of Buenos Aires, seems to be the leader, are uncovering numerous infestations with *Fasciola hepatica* widely scattered throughout the world). It passes a portion of its life in the body of a small snail and later penetrates into a certain species of small fish in whose muscles it becomes encysted. When this fish is eaten raw the parasite is introduced into the intestinal tract of man and the other animals which harbor it, whence its eggs finally issue to complete the vicious circle. It seems possible for the majority of individuals to remain apparently healthy, though the bile ducts, and occasionally even the pancreas and duodenum, are considerably infested with this fluke. In 367 consecutive autopsies on adult Chinese in Hong Kong

Uttley (1935) found clonorchis present in 52 instances, but in no case had the fluke been the cause of death. When symptoms arise they are the following: gastro intestinal pain and tenderness, nosebleed, jaundice and bloody diarrhea, in severe cases edema, ascites, anemia, and death from cachexia.

THERAPY

The anthelmintic drugs have been usually considered a complete failure in the treatment of liver flukes, but Kouri and Valverde (1935) reported the successful use of emetine in 2 cases (methods of employing this drug in Amebic Dysentery). Shattuck (1924) used tartar emetic (as in Kala azar) and the arsphenamines in 6 asymptomatic cases, and wrote 'The facts seem to indicate, first, that both tartar emetic and arsphenamines are somewhat poisonous to clonorchis, and second, that it may be advantageous to give them in successive courses'. Kingasa (1939) found fuadin (see Bilharziasis below) superior. Faust (1939) says that gentian violet, crystal violet or methyl violet may be helpful, oral dosage in enteric coated pills is 30 mg every other day and not to exceed a total of 300 mg /Kg. Manson Bahr (1940) says that spectacular results sometimes follow duodenal tube bile drainage, a practice which seems to be widespread in Korea.

LUNG FLUKES

The fluke, *Paragonimus westermani*, infests dogs, cats, pigs, rodents, and the larger carnivorous animals over a wide range. It is also established as a human parasite throughout a wide territory in the Far East, in central Africa, Peru and Venezuela. Faust (1939) says that reports of autochthonous cases in Mexico are apparently erroneous. Likewise, no truly autochthonous cases have occurred in the United States, though animals are infested with the closely related species, *P. hellicotti*, throughout a wide territory in our country, according to Ameel (1934), the usual mammalian host here is the mink. The fluke passes a part of its life cycle in the body of a snail and finally is taken up by a fresh water crab and crayfish. When these mollusks or crustaceans are eaten uncooked, or the water in which they have disintegrated is swallowed, the metacercarian form of the fluke works its way through the tissues intervening between the intestinal tract and the lungs in which latter organ it forms a cyst in which it undergoes full development. Not infrequently other organs or tissues, even the brain, are invaded. The pulmonary type of invasion is characterized by cough, frequent hemoptysis and signs of cavity. The eggs are present in the sputum or feces.

THERAPY

So far as I am aware no satisfactory treatment has been developed for this malady, though To and Ko (1935) have reported the partially successful use, in 4 cases, of 5 per cent carpane hydrochloride in normal saline, injecting subcutaneously. The total quantities used were respectively 0.3 Gm. over

six days, 1.1 Gm over twenty three days, 0.5 Gm over ten days, and 0.9 Gm over thirty days. Emetine is also used as in amebic dysentery (qv). Bercovitz (1937) reports some relief following the bronchial instillation of lipiodol in a small number of pulmonary cases.

BLOOD FLUKES

(Bilharziasis)

The disease which bears the name of Bilharz, who first wrote of it in 1852, is caused by four flukes, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, and *S. bovis*. The cycle of events is as follows: the eggs are discharged in the urine and feces of infested men or animals, in fresh water, motile larvae develop and enter certain specific snails, after about six weeks another form of larvae leave the snails and move about very actively in the water, it is these latter larvae that pierce the skin or buccal mucous membrane of persons or animals during bathing or drinking, and set up the disease. The venous system is quickly entered and in the larger portal vessels the flukes mature and become paired. In pairs (male and female) they then travel toward the periphery and become lodged in the submucosal veins of the intestines and bladder, where they deposit enormous numbers of eggs; more rarely the cerebral cortex, lungs and genital organs, especially the latter, are selected as sites for these fluke nuptial couches. The pathologic reactions consist in a cellular response to the general toxemia and a local inflammatory reaction to the presence of the aggregations of eggs; chronic inflammatory changes lead ultimately to fibrosis, especially in the liver and colon according to Koppish (1941).

When the larvae penetrate the skin there is for a short time an intense pruritus and erythema, then, after what may be termed an incubation period of three weeks, the toxic symptoms appear: malaise, headache, cough, chills and fever, and abdominal pain and tenderness which finally localizes over the liver region. The symptoms due to the local processes in the bladder and intestine usually do not appear until another three to twelve months have elapsed. In the intestinal cases the symptoms are not clear cut but there are usually recurrent attacks of bloody dysentery and colicky pain and tenesmus, there are palpable papillomata of the rectum and distinctive signs upon sigmoidoscopic examination. In bladder cases there is burning and frequent micturition, suprapubic aching, hematuria and urethral bleeding, and, perhaps in later cases, symptoms of cystitis and vesical calculus, tubercles and papillomata are found upon cystoscopic examination. There is a tendency for malignant growths to engraft themselves upon these local lesions. Cardiovascular and pulmonary involvement in bilharziasis has been described (Clark and Graef, 1935, Shaw and Ghareeb, 1938). Laboratory tests are of great assistance in the diagnosis: marked eosinophilia, the presence of ova in the stools and urine and in sectioned tissue from the bladder and rectum, and a positive complement deviation test as devised by Fairley.

Schistosoma haematobium causes the bladder type of bilharziasis. It pre-

vails in Egypt to an enormous extent and is apparently endemic throughout much of the rest of the African continent, as well as in Portugal, Spain, Greece, Cyprus, Palestine, Syria, Iraq, Iran, Arabia, western Australia, Madagascar and the two neighboring islands of Réunion and Mauritius. It seems that the proper snail host is not present in India and the Malay archipelago, thus accounting for the freedom of these pestilential regions from at least one of the more dire maladies. Experiments a few years ago in Corsica, which was still free from infestation prior to the outbreak of World War II, showed the ease with which colonial African soldiers coming from regions in which the disease is endemic may infect the mollusks in that island. *Schistosoma mansoni* occurs quite generally in Africa, cases in Egypt for instance, being often mixed, *i.e.*, caused by infestation with both *S. haematobium* and *S. mansoni*. *Schistosoma mansoni* occurs alone also in Brazil, Venezuela and Dutch Guiana in South America, and in Antigua, Guadeloupe, Martinique, St. Kitts, St. Lucia, Nevis, Vieques, Montserrat, and Puerto Rico in the West Indies. *Schistosoma japonicum* occurs to a very considerable extent in rice growing districts in Japan and in the Yangtze Valley in China, in scattered foci along the coast and also inland in southern China, and in Formosa, cases are also being reported in the Philippines and the Celebes (Sandground and Bonne, 1940). I believe the only reported cases of human infestation with *S. bovis* have been in Natal, southern Rhodesia and in the Belgian Congo. Cutler, reviewing the literature in 1926 collected 22 imported cases of schistosomal infection in North America, Hoff (1936) has added 2 others.

Spontaneous cure is undoubtedly effected in some cases of bilharziasis after a variable length of time and it is often stated that ova cease to be passed in the urine and feces of an individual after three years of residence outside an endemic center. However, in Cutler's review it is clearly shown that both clinical and laboratory evidences of the disease may persist for ten or more years of consecutive residence in a nonbilharzial country.

THERAPY

Tartar Emetic—It is only since 1918, when Christopherson introduced the use of tartar emetic, that we have been able to speak of having a specific remedial agent in this disease. Subsequent reports have all been in agreement that the drug is remarkably effective. The most recent authoritative statistical report is that of Khalil (1935), whose percentage of cures in 1000 consecutive patients completing the course of 14 to 17 injections was 89.4. A few days after beginning treatment general clinical improvement begins and the number of ova in the urine or feces is considerably decreased. At the end of the first week there is an increase in the number of ova but many of them appear granular and black, and after two weeks half of them are obviously dead, at the end of the third week all are usually dead. Christopherson admitted that granular ova are passed in cases not undergoing treatment but pointed out that the number is never so large as in the treated cases. He believed that tartar emetic kills the ova as well as the embedded flukes. If treatment has not been entirely successful, reexamination will show ova within a month or six weeks, whereas if reinfestation has taken place, the ova will not reappear until three or four months have elapsed. Tartar emetic

is given intravenously, $\frac{1}{2}$ grain (0.032 Gm) being dissolved in 6 cc of sterile physiologic salt solution. Injections are given every second day and are increased by $\frac{1}{2}$ grain (0.032 Gm) on each occasion, though it is considered advisable to give no more than $2\frac{1}{2}$ grains (0.16 Gm) at any one time. Indeed many patients will show signs of intolerance on much smaller doses than this (see Kala azar for symptoms of tartar emetic intoxication). A total of 25 to 30 grains (1.63–2 Gm) for the adult perhaps no more than 10 grains (0.6 Gm) for children is needed for complete eradication of *S. haematobium* and *S. japonica* cases. Manson Bahr (1940) believes that much more than this is required in *S. mansoni* cases.

Bongenault reports a patient who was very intolerant to the drug when given intravenously but who bore it very well when given by the rectum. He states that six daily enemas of 4 grains (0.25 Gm) of tartar emetic in 50 cc of water were sufficient to effect clinical and laboratory cure. This is very astonishing in view of the fact that students of kala azar have not been able to obtain satisfactory rectal absorption of the drug in that disease.

Fuadin—This drug which is one of the newer antimonial preparations has been in use since 1929. Khalil and his associates early reported more rapid 'cures' than with tartar emetic. The treatment consists of 9 to 13 intramuscular injections beginning with 1.5 cc of the commercial solution and increasing in injections every two days, to 5 cc at the third injection and finishing the course at that dosage. In the most recently reported (1936) series of 3302 cases 63.4 per cent were cured after 9 injections, 78.6 per cent after 11 injections, and 83 per cent after 13 injections. The great advantages of the drug over tartar emetic are that it is given intramuscularly and causes very little pain at the time of injection or later. The alleged superiority in the matter of relative freedom from toxicity is still matter for debate. Khalil (1936) is studying a method of detecting the patient who is hypersensitive to the antimonials before treatment has progressed very far but Diamantis (1938) considers the test impractical so far.

Acridavine—Fisher (1934) has reported a certain amount of success with this drug given by mouth but subsequent reports (Khalil and Salah 1934, Fakhry, 1934) have failed to substantiate his findings though it may be that a satisfactory dosage will still be developed.

Emetine—Tsykalas in 1933 celebrated his introduction of this drug into the therapy of bilharziasis twenty years earlier by publishing his notes on 3800 cases. The dosage he states should be 1.12 Gm in all given intravenously in 10 injections during two weeks: the first 4 injections of 0.1, 0.12, 0.14 and 0.16 Gm, and the remainder, 0.1 Gm. The dangers and precautions, contraindications, etc. with regard to emetine are discussed under Amebic Dysentery. I am unable to find that anyone agrees with Tsykalas that emetine is superior to other drugs though all observers readily admit its greater toxicity.

PROPHYLAXIS

The best method of preventing the occurrence of bilharziasis would be to eradicate the disease in all infested men and animals by the proper employment of the specific drugs but this is of course a practical impossibility. The next choice among prophylactic measures is to seek the destruction of the snail which serves as intermediate host. Sufficient advances have been

already made in this direction to show that it is a practicable means of fighting the disease in some regions, but in other infested areas there are immense obstacles to be overcome before success can be hoped for. The subject is an extremely interesting and important one, but as it involves principally large-scale projects in sanitation, a discussion of it would probably be out of place here.

Of course no drinking of, or wading or bathing in fresh water in areas of bilharzial endemicity should be indulged in. Suspected drinking water may be rendered safe for use by storing it in snail-free tanks for forty-eight hours or more, for most of the larvae perish unless they enter the human host within twenty-four hours after they leave the snail and all of them are dead at the end of forty-eight hours. Sandbed filtration is not effective against them but Berkefeld and Pasteur Chamberland filters hold them back. The ordinary chlorination of drinking water does not destroy schistosome larvae. Water for washing and bathing purposes may be rendered safe (according to Leiper) by the addition of cresol in the proportions of 1 : 10,000.

SCHISTOSOME DERMATITIS

("Summer's Itch")

For a good many years there have been increasing complaints from waders, bathers and swimmers in the lakes of the north-central part of the United States of a severe form of itching which attacked them after leaving the water. In some of the worst years the summer tourist trade has been considerably affected by this "swimmer's itch." A similar disturbance troubles swimmers in Great Britain and on the Continent also. Not every person in a bathing party is affected, though the exceptions are in the majority; children are the most frequent and most severe victims. In a typical case the itch is fully developed in half to one hour after leaving the water and is followed in a few hours by a scattered pin-point macular and then papular rash. When the lesions are mature they much resemble bigger bites and of course may become secondarily infected from scratching. The itching frequently increases greatly at night but ordinarily disappears in about three days, the lesions often requiring several weeks to fade out. In 1923, Cort, of Johns Hopkins University, determined this malady to be due to penetration of the skin by the free-swimming larval forms of certain schistosomes. Cort has subsequently contributed much to further the understanding of the subject and in recent years in my own state of Wisconsin, Brackett and his associates at the University of Wisconsin have considerably added to our knowledge. Of a number of schistosomes which might be the active agent in this country, it seems that *Cercaria stagnicolae* is the principal offender though, according to McMullen and Brackett (1941), in a few instances *C. elvae* and *C. physellae* have been convicted. What happens is this: the eggs of this fluke are dropped into the water in the feces of some animal unknown (but considered most likely to be one or more migratory birds), they develop into embryos which enter the bodies of snails, after

awhile in the snails a free swimming larval form emerges (the cercariae) and goes about in the water searching its natural host, the birds, having entered and penetrated into the blood vessels of which, they make their way into the intestinal veins so that the eggs may be deposited in the water as above described, but if a human being is in the water and in the path of these cercariae they strive to enter his body, their presence in the skin giving rise to the itching and the visible lesions Brackett's (1940) histologic studies show that the organisms are destroyed in the epithelial layers of the skin and probably do not reach the deeper tissues, so there is no warrant in present knowledge for the fear that a systemic form of schistosomal infection will result from one of these attacks

THERAPY

Ridding lakes and bathing beaches of snails by the use of copper sulfate or carbonate or formaldehyde additions to the water has not proved an entirely practicable measure as yet Brackett (1939) has shown that the best protection against an attack is to rub down the body vigorously with a towel after leaving the water—not soon after leaving but at once, for there is evidence that most of the penetration takes place when evaporation begins, for this reason children who are paddling in and out of the water frequently are the most severely affected

Antipruritic lotions (see Index) are usually the only agents indicated in treatment

WORM INFESTATION

WORM INFESTATION

TAPEWORMS

The principal tapeworms infesting man are *Taenia saginata*, *T. solium*, *Hymenolepis nana*, and *Diphyllobothrium latum* (*Bothriocephalus latus*). The following have also been occasionally recorded: *Hymenolepis diminuta*, *H. lanceolata*, *Diphyllobothrium cordatum*, *Dipylidium caninum*, *Diplogonoporus grandis*, and *Darainca madagascariensis*.

Taenia saginata, the beef tapeworm, occurs all over the world wherever beef is eaten, it and *Hymenolepis nana* are the two most common tapeworms in the United States and Canada. It attaches itself to the upper part of the intestinal tract of man only, usually but one worm being present at a time. The larvae encyst in the muscular tissues of cattle, and it is the eating of these tissues raw or insufficiently cooked that introduces the parasite into its human host. If beef is solidly frozen the larvae die within six days and they die also in ordinary cold storage of three weeks' duration, but in the latter case their death is due not to the low temperature but to the fact that they are unable to survive the death of their host for a longer period.

Hymenolepis nana, the dwarf tapeworm, is quite common throughout the world though it particularly favors the warmer climates, in the Western Hemisphere it shares the honors with the beef tapeworm. It is acquired by the direct swallowing of the ova from an infested individual and is especially frequent in children. There is some presumptive evidence that the rat flea may act as intermediate host by harboring the larval stage of the worm.

Taenia solium, the pork tapeworm, on the whole infests man much less frequently than the beef tapeworm but is rather common in parts of South America, India, Egypt, and Malaya and also occurs in somewhat circumscribed areas elsewhere in both hemispheres, in North America it is of very infrequent occurrence. The larvae are encysted in the tissues of pigs and pass into the human intestinal tract when this 'measly' pork is eaten raw or insufficiently cooked. Infested pork is not rendered safe for human consumption by cold storage or even by freezing. The larvae are also harbored in deer, bears, monkeys, dogs and cats. Man can become infested with the larvae by eating foods contaminated by another infested individual, as it does not seem necessary for the larval stage to be passed in another animal, he may also reinfest himself if a ripe proglottis happens to pass upward into the stomach, where it will liberate its ova. The larvae sometimes enter the blood stream and, becoming encysted in the tissues, give rise to the entity known as 'cysticercosis' with a variegated array of symptoms, death of such encysted larvae in the brain, followed by the liberation of the toxic products of their dissolution may give rise to symptoms indistinguishable from those of idiopathic epilepsy. The adult worm develops only in the intestinal tract. Multiplicity of worms is not the rule but the occurrence of more than one is more frequent than with the beef tapeworm.

Diphyllobothrium latum, the broad or fish tapeworm, is common in Japan, Turkestan, Roumania, Poland, Switzerland, many parts of Africa and particularly in the countries bordering upon the Baltic Sea. The eggs

of this tapeworm hatch in water and the larvae enter the bodies of certain small crustaceans, fish are infested by swallowing the crustaceans and man by swallowing uncooked, the fish. Neither smoking nor salting will destroy the larvae only thorough cooking will do it. The adult worms develop in large numbers in the intestinal tract of man, dogs, pigs, cats, foxes, and perhaps all other fish-eating animals. They are very long lived, a case being on record in which one of these worms was harbored for sixteen years. It is therefore not remarkable that the western portion of the Great Lakes region of the United States and Canada, so largely populated by immigrants from the Baltic region, has finally come to be recognized as an endemic focus for the dissemination of the larvae of this worm. Warthin, in 1897, warned that this might be expected and his later observations and those of Vergeer have proved how true was the prediction. At least 4 species of food fishes have been already inculpatated. It seems that these are taken commercially in only very small amounts from the contaminated portion of Lake Superior, but Vergeer believed that infestation would spread through the shipping east for the Jewish trade of large amounts of fresh fish from Lake Winnipeg, Lake Manitoba, Lake of the Woods and Lake Winnipegosis, subsequent observations have shown that human infestation is increasing in the eastern portions of the United States and Canada. Essex (1938) found that in a small lake in Minnesota the level of infestation of the fish remained about what it had been in 1930.

Tapeworm infestation is said to be manifested by any or all of the following symptoms: abnormal appetite, picking of the nose and scratching of the anus, restlessness at night and a large array of nervous symptoms by day, vertigo and a sinking sensation, anemia, a sensation of weight in the epigastrium, attacks of colicky abdominal pain, nausea and vomiting and ova in the stools. The ova can always be found if the microscopist is an expert and is not satisfied with a single examination. In the case of *Taenia saginata* segments often wander out of the anus when the patient is not at stool so that he soon becomes aware of his malady, segments of the other members of the group are usually passed unnoticed with the feces. In individuals harboring *Diphyllobothrium latum*, the blood picture sometimes closely resembles that of pernicious anemia. Mackie (1939), in the United States, says that the occurrence of such a picture in these patients more often than in individuals not so infested is not a fact, but von Bonsdorff in Finland where great numbers of these cases are seen is still very closely studying the matter and when he last reported in 1940 seemed still of the belief that such anemias are at times caused by the worms. However, it cannot be too strongly impressed upon the reader that his patient may harbor any of the tapeworms and manifest no symptoms whatever. To examine the stools of any individual whose symptoms are of a vague nature is good practice.

THERAPY

In the treatment of a patient infested with any of the tapeworms several things are essential to success. In the first place, the intestinal tract must be thoroughly cleaned out in order that the vermifuge may have free to the parasite. The work of Macht and Finesilver has shown that nesium sulfate is the best cathartic to employ for this purpose since

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THERAPY

In the treatment of a patient infested with any of the tapeworms several things are essential to success. In the first place, the intestinal tract must be thoroughly cleaned out in order that the vermifuge may have free access to the parasite. The work of Macht and Finesdver has shown that magnesium sulfate is the best cathartic to employ for this purpose since for

several hours after its use the absorption of all other drugs is much retarded. Second, the dose of the vermifuge must be large enough to stun the worm only, for a dose large enough to kill him is somewhat dangerous to the patient. Death following the use of these vermifuges is rare, but great depression and even collapse are not infrequent, therefore the patient should be caused to stay quietly in bed throughout the course of the treatment. Third, the dose of the drug must be followed by another saline purge in order to sweep out the worm and the remnants of the drug. Fourth, careful search must be made for the head. If the treatment has been successful it will nearly always be found if properly searched for by the physician himself, though it sometimes is discharged separately within the next few days, or it may be digested and not discharged at all, the latter occurrence is probably very rare. In any case, if ova continue to be passed in indication that the treatment has failed, it should not be repeated in less than one month and in weakly individuals not for a much longer time.

The toxicology of vermifuges is presented at the end of this chapter. It is probably well not to employ any of these drugs during pregnancy—pumpkin seeds are the exception as these seem to be harmless under any conditions.

Aspidium (Male Fern)—The usual dose of the oleoresin of aspidium as gauged for children is 0.5 Gm. per year of age, but not to exceed 5 Gm. Indeed, even in an adult it is doubtfully advisable much to exceed this latter dose. The substance is extremely disagreeable in taste and is difficult to disguise. The following prescription, which is for a child of five, is about as satisfactory as any.

R̄ Oleoresin of aspidium	gr. xl	2 0
Fluidextract of glycyrrhiza	℥iiss	10 0
Syrup of orange flowers	℥v	20 0
Peppermint water to make	℥ij	60 0
Label To be taken in 1 dose		

Magath and Brown, of the Mayo Clinic use the following emulsion for an adult.

R̄ Oleoresin of aspidium	℥iiss	6 0
Powdered acacia	℥ij	8 0
Water to make	℥ij	60 0

They direct that the patient should omit luncheon and supper on the day preceding treatment though black coffee, tea and water are allowed. At 6 P.M. a dose of magnesium sulfate is taken and this is repeated at 6 A.M. next morning. Then, without breakfast and after the bowels have moved half the dose of the drug is given, one hour later, the other half. After two more hours, another dose of magnesium sulfate, and two hours after this a large soapsuds enema. The stool is then passed into a container, but the toilet paper should be separately disposed of. In searching for the worm head the top half of the stool is poured off and the rest poured through a 20 mesh sieve, followed by warm water, so that the sieve will contain only the worm. The worm is then rinsed out into a pan with black painted bottom to facilitate search for the head.

It is now no longer held to be true, according to Travell (1939), that castor oil increases the toxicity of aspidium.

All of the other vermifuges are used, of course, to eliminate the tapeworm, but I believe that none are as often effective as aspidium. The following are those with perhaps the best record.

Pumpkin Seeds (Pepo).—Pumpkin seeds not over a year old, and the fresher the better, have definite anthelmintic value. Thirty to 50 Gm., according to the age of the individual, has been considered the standard dose in the past, but Krayer (1937) says that doses much larger (he used up to 200 Gm. for an adult) must be used in order to obtain best results; in short there is apparently no harm in giving all the patient will accept. The seeds are reduced to a paste in a mortar and rubbed up with sugar and perhaps a little honey. It is said that children like this mixture, to which a little milk may be added if desired.

Pomegranate Bark (Granatum).—From 50 to 60 Gm. of fresh bark are thoroughly bruised in 750 cc. of water and allowed to stand for twelve hours; this is then boiled to about 500 cc., cooled, a little syrup added, and administered. An effective remedy but one which is nearly always vomited. Half this dose is sufficient for children.

Pelletierine Tannate.—This is a mixture of several alkaloids of the above bark and is easier to give since the dose is small, being only 4 grains (0.25 Gm.) and it can be easily suspended in simple syrup. This is considered by many practitioners to be the most surely effective of all the vermifuges available for the treatment of tapeworm, but it is too toxic for any but very robust individuals and it should perhaps never be given to children.

Carbon Tetrachloride.—Sandground (1938) reported the successful use of this drug in a small series of cases (see methods in Hookworm), and Mackie (1939) also spoke well of it; there have been earlier favorable reports but the drug has not been widely adopted for use in tapeworm.

"Early Bird."—This concoction, still employed in some hospitals is prepared as follows:

Pumpkin seed	8 Gm.
Cusso	4 "
Pomegranate	4 "

Make an infusion, to which is to be added

Kamala	4 "
Oleoresin of aspidium	4 "
Glycerin	15 cc
Mucilage of acacia	15 "
Water to make	240 "

This quantity is taken in two drafts two hours apart, after the usual preliminary treatment. Bastedo says: "The 'early bird' usually gets the worm," but he has several times seen severe gastro-intestinal irritation with vertigo and prostration result from the use of this mixture.

Transduodenal Treatment.—Sokolovski (1933) reports success in promoting expulsion of the worm and head in thirty to sixty minutes in 10 of 11 cases in which he administered 15 grains (1 Gm.) of quinine (the salt used is not stated) in 10 per cent alcoholic solution by duodenal tube; the quinine was followed down the tube in five minutes by 15 cc. of 25 per cent magnesium sulfate solution. Golob (1935) has administered aspidium emulsion simultaneously with 30 cc. of saturated solution of magnesium sulfate

by the tube in a single case, the mixture was vomited despite the fact that the tip of the tube lay in the second portion of the duodenum but the vomitus was saved, kept warm, and later reintroduced with the addition of more magnesium sulfate solution. The worm was expelled with head intact. Clements (1935) has reported a very recalcitrant case in which he felt justified in performing an appendicostomy, inserting a catheter, and flushing the intestine out with 1 per cent solution of iodine, the head of the worm came away within five minutes and the patient recovered and remained free of symptoms of infestation.

HYDATID DISEASE

(*Echinococcus Disease*)

Taenia echinococcus is a small tapeworm of the dog and his congeners the jackal, the wolf, etc., more rarely it is contracted by other carnivorous animals. The ova are spread in the feces of the infested dog and are also deposited upon the objects which he licks with his tongue. Grass-eating animals such as cattle, sheep, pigs, deer, moose (but not, according to Barnett, 1939, the rabbit) take up the ova with their food and act as secondary hosts for the parasite, when the dog eats the uncooked viscera of these animals he acquires the larval form of the worm, and so the vicious circle is perpetuated. Man may acquire the ova by too intimate association with infested dogs, or much more rarely by ingesting uncooked contaminated vegetables or drinking water. The embryo is freed by the digestive juices in the stomach, passes down the intestine, is taken up by the portal vein and passes to the internal organs where the larvae in developing cause the condition known as echinococcus disease. The liver is the stopping place for the parasite in about 75 per cent of the cases, the lung in about 9 per cent, and all the other organs and tissues combined in about 16 per cent.

Since a pathologic description of a hydatid cyst is not within the province of this book, it must suffice here to say that the ultimate form of this cyst is a brood capsule which contains, if not secondarily infected, a crystal-clear fluid and a great many scolices or rudimentary worm heads, there are usually quite similar cysts within the cavity of this primary cyst, and even these secondary cysts may themselves contain cysts. The symptoms are those of a characteristic tumor in an individual not otherwise greatly affected in health. X ray, the complement deviation and the intradermal tests are of great assistance in making the diagnosis. Of course if rupture takes place into any of the body cavities, the symptoms of shock and collapse are to be expected. After such a rupture a new crop of cysts may develop in great number. If a cyst becomes infected, which often takes place through the bile ducts apparently, the picture of sepsis plus jaundice and often urticaria is superimposed. In regions where the disease is frequently encountered it is not often confused with other entities, such as malignancy, tuberculosis etc., but where hydatid disease is unusual the diagnosis is rarely made outside the operating or autopsy room.

At the present time echinococcus disease is most prevalent in Australia New Zealand, the Argentine, Uruguay, Cape Colony, southern Brazil, Mecklenburg, Pomerania, Bavaria, Switzerland, Iraq Iran, Austria Yugoslavia Hungary, Dalmatia Bulgaria, Greece, Turkey, Egypt, Russia, Siberia, Morocco, Palestine, Syria Roumania France Italy Wales and Iceland For most of the world there are no reliable figures available Maplestone (1933) believes that the incidence is higher in India than the literature would indicate Hinshaw (1937) states that in Syria the disease is one and one half to three times as common as in Australia and New Zealand four times as common as in Egypt and ten times as common as in Iceland Magath (1937) says that at least 482 cases have been recorded in Canada and the United States since the first case seen in 1808 of these patients only 3 had likely acquired the infection in Canada and 19 in the United States, in 1938, Sawitz reported another autochthonous case in the United States

THERAPY

I am unable to find any satisfactory evidence that either drugs or biologicals are of the least value in the treatment of hydatid cyst Direct surgical attack, on the other hand is often productive of most excellent results Theoretically, the use of the x ray would be indicated but the work of Dévé has conclusively shown that its employment is impractical for the reason that the scolices within the cysts succumb only to a dose of the ray which would be highly injurious to the tissues of the patient

PROPHYLAXIS

In Iceland, which has been a great sheep raising country for over a thousand years, hydatid disease reached its highest incidence about 1867, since which time a remarkable drop has occurred Ofeigsson (1937) lists the following prophylactic measures as having effected this change (1) the decrease in poverty with increased freedom from a foreign rule and especially since Iceland became a free country, (2) better hygiene, (3) Krabbe's discovery in 1863 of the life cycle of the echinococcus, (4) the rapid spread of the knowledge of this discovery among Icelandic doctors and laymen, who realized the importance of breaking the life cycle of the parasite, (5) more and better doctors (6) laws forbidding all unnecessary dogs, resulting in a great reduction of their number, (7) a quarantine for two days, once or twice a year of all dogs during which they are treated with baths and suitable drugs (8) warnings to people against too much petting of their dogs and careful washing of their hands after touching them, (9) laws forbidding farmers to slaughter their sheep on their farms and permitting only authorized slaughter houses which are supervised rigidly (10) inspection of all meat by veterinary surgeons and (11) burning or burying of all infected organs of sheep and cattle According to Barnett (1941), in spite of a similarly intensive preventive campaign, the incidence of infection has not yet begun to wane in New Zealand

Turner (1933) and associates have reported the artificial immunization of dogs with some success through injecting an antigen obtained from cysts Penfold (1938) failed in an attempt to immunize lambs

THE COMMON ROUND-WORM

Ascaris lumbricoides is the intestinal worm most commonly infesting man. It is quite ubiquitous but in cool climates is encountered principally in children. In the tropics, however, and in many regions of poor sanitation in northern latitudes, the incidence is very much higher and the worm occurs in individuals of all ages. In China, and other countries where the Chinese custom of employing night soil in vegetable gardens prevails, it is also harbored with a frequency which is astonishing to practitioners in Europe and North America, in Egypt, about 6 of the 15 million people harbor this worm, average prevalence in the Nile delta itself being as high as 80 per cent (Scott, 1939).

This parasite needs no intermediate host for its full development. When the egg is swallowed by man it hatches in the small intestine, migrates to the liver and then to the lungs, from the latter situation it passes up the trachea and down the esophagus and through the stomach to settle down to maturity in the small intestine. An individual usually harbors from four to six of the adult parasites but sometimes the number is much greater than this. Any, many, or no symptoms may herald the presence of round worm, the infestation is most often diagnosed by suspecting its presence, i.e., searching for the ova in several stools. When an individual harboring round worms develops fever, as during the course of one of the infectious diseases, the worms seem to be disturbed and show some tendency to wander from the intestine into the stomach, esophagus, upper air passages, bile ducts, or even more distant parts of the body. Remote wanderings are very rare, however. Christie found only 10 instances of migration in a study of 800 postmortem reports of round worm cases. Their liability to complicate laparotomy cases is of more importance and should be taken into account in all regions of heavy infestation. Ludlow's experience in Korea has shown him the advisability of routine anthelmintic treatment prior to surgical procedures in all cases in which it is not definitely contraindicated.

THERAPY

Hexylresorcinol.—As a result of the studies of Lawson and his associates, in 1931-1932, this drug has come to be the preferred one on the basis both of efficacy and relative nontoxicity. It is used in the following dosage: 6 grains (0.4 Gm.) to very young children, 10 to 12 grains (0.6 to 0.8 Gm.) to those from six to twelve years, 15 grains (1.0 Gm.) above twelve years. Smilie (1939) says that the best method is to give the drug early in the morning on an empty stomach, followed within an hour to an hour and a half by a saline cathartic, and then no food to be taken until noon. Often there have been complaints of slight burning gastric irritation and occasionally a patient vomits but no reactions of more serious moment have been recorded. The drug was first made available in crystalline form in hard gelatin capsules but it was said that a reaction often occurred between the active agent and the gelatin (particularly in warm, moist climates), an occasional superficial burn of the mucosa of the mouth was also seen if children chewed the capsules. The first substitute for these capsules was the familiar sugar-coated pill, but as this can also be chewed a new form has now been found, an 'iron bound' capsule which is said to be impossible to chew.

Oil of Chenopodium—Oil of chenopodium won a place for itself in round worm therapy on the basis of efficacy but did not hold it long after hexyl resorcinol was made available in a satisfactory form for administration (see Hookworm for methods of using oil of chenopodium) *i.e.*, hexylresorcinol is preferred in private practice but in mass administrations in field work the drug is much too expensive and there oil of chenopodium has still to be preferred. Similie (1939), while admitting indeed even stressing the potential toxicity of oil of chenopodium, and much preferring to use hexylresorcinol wherever possible, nevertheless still looks upon the oil as the more effective drug.

Santonin—This is the oldest of the remedies for round worm infestation and it is still much used because, being insoluble outside the intestinal tract and practically tasteless it may be easily administered to children by incorporating the dose with a little sugar. Calomel, given to lessen absorption and to sweep out the stunned worms may conveniently be added to this mixture the commercial tablet (omitted from N.F. VI, for reasons unknown to me) containing $\frac{1}{2}$ grain (0.03 Gm.) of the drug and an equal quantity of calomel is so pleasing to children that they will eat too many of the tablets if the supply is not carefully guarded. Ransom, in his excellent treatise on the intestinal parasites of man, wrote of the use of santonin as follows:

It may be given in a dose of 1 to 3 grams (0.065 to 0.2 Gm.) to adults mixed with an equal quantity of calomel or to children at the rate of $\frac{1}{2}$ grain (0.01 Gm.) per year of age, also with calomel. This dose is given two or three days in succession and the treatment repeated in about ten days if eggs are still present in the feces. Castor oil may be substituted for the calomel in a dose of from 1 drachm to 1 ounce (4-32 cc.), depending upon the age and size of the patient, latterly, however, there seems to have arisen some doubt (Brown 1934) of the safety of using the oil. If neither calomel nor castor oil has been used it is well to give a dose of magnesium sulfate several hours after giving the santonin. Preparatory semi starvation is not so necessary with this drug as with some others, Hall (1930) gave it several hours after breakfast, with calomel. Brown, late at night after a light supper, with calomel and with a magnesium sulfate purge also in the morning.

Very large doses of santonin have often been given without untoward results, while small doses have not infrequently caused severe poisoning. It is a tricky drug and it is doubtful if one can with impunity exceed 3 grains as the maximum adult dose. I have so often recounted to my students an astonishing and illustrative experience which befell me during a brief sojourn as ship's surgeon in the tropics that I would feel quite remiss if I failed to place it on record here. One day, off the coast of Ecuador, a Mexican fireman appeared at my door and announced that he had 'borned a bug'. Being entirely without understanding of his meaning, and furthermore altogether fearful of the volubility which I knew would greet an attempt to question him in my sorry distortions of his native language, I merely signified a desire to be led to the scene of this delivery. Whereupon he promptly conducted me to the after part of the main deck, where, surrounded by a gleeful group of his fellow-countrymen, a large round worm lay in the seuppers. And before I could quite realize the significance of the scene, he began obligingly to cough and retch—and in a moment with the assistance of two fingers inserted into his throat he had brought up another! But now for the

illustrative part of the tale, so far as it concerns the drug under discussion. This man gave a history of malaria which had been 'cured' two years before, and was certainly not suffering from any sort of febrile disturbance at the time of this incident, furthermore, at the examination of the crew six weeks previously, and often in deck encounters since, I had remarked him as an exceptionally robust and hearty fellow. I therefore gave him 5 grains of santonin, 3 grains of calomel and a little sugar—with the result that within the hour he was in convulsions, from which he went into coma, and only escaped foregathering with his Aztec fathers because they seemed not quite ready to call him in. Moral to adorn a dull tale: never give 5 grains of santonin to any man alive if it is desired that he continue in that condition.

THE PIN-, THREAD- OR SEATWORM

Enterobius (Oxyuris) vermicularis is a frequent infester of the anal region in infants and young children all over the world but perhaps most frequently in the warmer climates. Adults do not harbor this worm so often as children do, and among the latter it is more commonly encountered in the city than in the country. An intermediate host is unnecessary, the entire life cycle being passed within the infested individual. The vicious circle is as follows: when the eggs are swallowed, the worms hatch and develop in the small intestine and appendix, but when mature they pass down to the lower part of the large intestine, when the females are ready to deposit their eggs they crawl out of the anus and wander about the perineum, even entering at times the vagina, the crawling of the worms in the rectum and on the perineum causes intense itching, in the process of scratching many of the females are crushed and their eggs liberated, the hands, contaminated with eggs, are ultimately carried to the mouth, and the whole circle is completed with the reinfestation which thus takes place. Recent studies have also shown that viable eggs contaminate the lower objects in rooms also such as furniture legs, rugs, window ledges, etc. Severe anal pruritus is the only definite symptom of pinworms, though it is perhaps not entirely incorrect to ascribe some of the nervous disturbances of young children, especially those with erotic manifestations, to this infestation. Some observers believe that the worm is responsible, directly or indirectly, for many cases of appendicitis, but this is certainly not proved though the worms are many times found in that appendage when it is removed. Diagnosis is made upon finding the eggs in the feces by the salt flotation method, but the more frequently employed method nowadays consists in applying an NIH swab to the perianal region (a glass rod to which is attached a small square of cellophane, this is stroked outward over the perianal mucosa and the cellophane square is then transferred to a glass slide and examined under the microscope). A single such examination is from 40 to 50 per cent efficient, many observers have confirmed the finding of Sawitz *et al* (1939) that seven such swabbings, on alternate mornings, will detect practically 100 per cent of infestations.

THERAPY

The length of the life cycle of the pinworm, from the time the eggs are ingested to the time the females crawl out the anal opening was formerly held to be a little more than two weeks. If therefore the conveyance of eggs from anus to mouth by contaminated fingers could be *absolutely* prevented for a period of two to three weeks it was thought the infestation would be cured. Now, however, with some investigators maintaining that the cycle may be several months in length and others that in some instances the eggs may be laid within the bowel and the cycle be completed there the hope of curing the patient with hygienic measures rigidly maintained during the period covered by one complete cycle is waning. However I shall continue to describe the methods even though the feat is extremely difficult of accomplishment none the less so because viable eggs are now known to survive quite a while on carpets furniture etc.

The treatment should begin with a full bath with soap and water, special attention being paid to the anal region. After this the anal region and perineum are to be anointed with an ointment composed of 2 per cent of ammoniated mercury in equal parts of lanolin and petrolatum a pad of cotton applied and the child clothed in heavy drawers that are closed front and back. After each defecation the anal region is to be thoroughly washed with soap and water the ointment and a fresh pad applied and the drawers put on again. At night, when the itching is at its worst the following anesthetic preparation may be substituted for the mercury ointment.

R Ethyl aminobenzoate (benzocaine)	gr xlv	3 0
Salicylic acid	gr xij	0 75
Hydrous wool fat (lanolin)	℥ss	15 0
Petrolatum to make	℥j	50 0

It may be necessary to tie the hands, especially at night, so that they cannot be carried to the site of itching. In any case, the cleansing of the hands is of the utmost importance since ordinary washing will not suffice to rid them of the eggs. They must be *thoroughly and frequently* scrubbed with brush, soap and water and the nails kept scrupulously clean. Daily full baths are desirable. If several children are closely associated all must be simultaneously treated else mutual reinfestation will be certain to take place. Bed sheets should be boiled at least twice weekly.

It is believed that a low carbohydrate diet is of advantage in these cases but I know of no careful studies showing that this is true.

Internal Medication—It is the usual practice to use vermifuges by mouth in the treatment of pinworm but their record in the past has not been brilliant. The newest agent to be employed is geotian violet it will be interesting to see what its fate will be. Wright and Brady (1940) have treated 224 patients with this drug giving adults 2 enteric-coated tablets of $\frac{1}{2}$ grain (0.03 Gm) three times daily before meals and children $\frac{1}{4}$ grain (0.01 Gm) a day for each year of apparent (not chronological) age the total daily amount of the drug for children being also divided into three daily doses. Their best results were obtained when the treatment was continued for two consecutive days. Nausea vomiting abdominal pain diarrhea headache and dizziness sometimes accompanied this medication but subsided

quickly when dosage was reduced or the drug was omitted for a day or two Brady (1941) says that the contraindications to gentiana violet therapy are concomitant infections with *Ascaris lumbricoides*, gastro intestinal, cardiac, hepatic, or renal disease, and pregnancy Alcohol should not be used during the period of treatment So far the record of success with this agent in the hands of several observers seems to be around 90 per cent

All the usual anthelmintic drugs—santonin, oil of chenopodium tetrachlorethylene, etc.—have been tried Wright *et al* (1937) succeeded in eradicating the infestation in about half of their cases with a single dose of tetrachlorethylene, for reasons not stated the dosage was only 0.1 cc for year of apparent age instead of 0.2 cc as commonly employed in combating hook worm Quinine by mouth has been quite efficacious in McAnally's (1937) admittedly limited experience Brown (1934) reported good results in a small series of cases in which he used hexylresorcinol both orally and by rectum He suggests the following treatment to be employed twice a week (a) omit breakfast, no food until noon, (b) hexylresorcinol pills orally 0.1 Gm per year of age up to ten years the ten year dose being the maximum, (c) drink plenty of water, (d) soapsuds enema and then an enema of 1 part crystalline hexylresorcinol in 1000 cc of water, to be given high and retained five minutes

Rectal Medication—The female oxyuris is difficult to discourage in her egg laying orgies about the anus Many formulae have been employed of which I can list but a few here, they are all intended for use every day or every second day over a long period of time The quantity administered should be sufficiently large that retention cannot occur though the patient should be instructed to resist expulsion as long as possible

Saline—Six per cent aqueous solution of sodium chloride (approximately 15 teaspoonfuls of salt to the quart of warm water)

Quassia—Two ounces (64 Gm) of the chips are to be added to 1½ pints (750 cc) of water and boiled down to 1 pint (500 cc), strained and introduced when cooled to body temperature This infusion may be made in saline, as above, instead of water

Salicylic Acid—The following formula is used

Salicylic acid	5ss	2 0
Sodium borate	3ss	2 0
Water to make	Oj	500 0

Introduce warm using half quantities for young children

Soap—The ordinary warm soapsuds enema is employed, many of the females are believed to be killed by 1 per cent soap solution

Vinegar—Ordinary table vinegar in the proportions of 30 to 100 parts to 1000 parts of warm water

Quinine—Any of the quinine salts may be employed in 1:2500 to 1:1000 aqueous solution The possibility, which is not at all remote of inducing cinchonism must always be taken into account

Hexylresorcinol—See Brown's method under *Internal Medication* above

WHIPWORM

Trichocephalus (Trichurus) trichiura is a very common worm all over the world, but is most frequently harbored in warm climates. Smillie states that it is probably the most widely distributed worm in the United States except the round worm, Moss (1939), in a routine stool examination of 2265 dispensary patients in New Orleans found it more prevalent than round-worm. No intermediate host is required to complete the life cycle of this worm. Infestation takes place when the eggs, which are distributed in human feces, are swallowed in contaminated water or upon uncooked food. The adult worms inhabit the cecum and appendix principally. *Trichocephalus* only very rarely causes symptoms and when they arise they are very variable, in Swartzwelder's (1939) analysis of his 81 uncomplicated cases the most frequent symptoms were abdominal, with also headache, backache, anorexia and loss of weight. For the most part, however, the worm seems to be harmless—if, as is extremely improbable, one is justified in considering harmless any parasitic invader of the body.

THERAPY

Probably the most effective substance for use against this worm is the fresh sap of a fig tree *Ficus laurifolia*, peculiar to certain river valleys of Colombia, where it is known as "Leche de Higueron." Fernan Nuñez states that it has been used for centuries by the South American natives and that he has employed it with very good results but that it is not generally used by physicians there because of the difficulty of obtaining it in sufficiently fresh state. Caldwell and Caldwell (1929) found that it would remove 85 per cent of the worms in a single treatment. Robbins (1930) isolated the active principle, ficin, but it proved to be a proteolytic enzyme which will attack and digest the stomach and intestinal mucosa if small lesions are present. The recent studies of Mohtor *et al* (1941), employing laboratory animals, do not indicate that the employment of ficin in its present form is likely to become a practicable measure. Of course all the other anthelmintics are employed but their efficacy is slight.

GUINEA OR MEDINA WORM

Dracunculus medinensis is a large worm that requires two hosts for the completion of its life cycle. The free swimming larvae penetrate and develop to a certain stage within the body of a very small crustacean of the genus *Cyclops*. When unboiled water containing this crustacean is swallowed man becomes infested. About a year after the ingestion of the larvae, the adult female worm works her way into the subcutaneous tissues in order to discharge her embryos outside the human body. Her presence is first manifested by the pruritus which is set up, then a cordlike lump can be felt beneath the skin, finally, there is a vesicle and then an ulcer, from an opening in the base of which the embryos are liberated in a milky fluid which exudes when cold water is brought into contact with the ulcerated surface. The

infestation of the primary crustacean host is easily accomplished by reason of the fact that most of the ulcers—there may be several in one individual—are upon the feet and ankles and are discharging continuously whenever the patient is wading through fresh water. There is a very pronounced eosinophilia but constitutional symptoms are slight.

Guinea worm is harbored in Arabia, Iran, Turkestan, and India, it is present in various parts of Africa, being particularly prevalent in the Nile valley, in South America, it is endemic in the Guianas and in certain districts in Brazil, it seems to be disappearing from the West Indies, which were formerly heavily infested, a few cases have been reported in the Netherlands Indies. It is of interest to note that Chitwood (1938) has found a worm morphologically identical with *D. medinensis* in the fox, raccoon, and mink in several parts of the United States and Canada, all the human cases reported on this continent have been imported, however.

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The natives everywhere effect the extraction of the worm by slowly winding it out around a small piece of wood. The process requires about two weeks and is open to the serious objection that if the worm breaks, as very frequently happens, secondary infection and a stubborn type of suppuration is almost certain to take place. Manson Bahr (1940) says that on the Gold Coast the natives rub the site of a presenting worm with olive oil and subsequently mercurial ointment daily and vigorously for a week or more, this is said to kill the underlying worm, which is then extracted. The orthodox physician's most usual method of attack is to inject 1-1000 solution of bichloride of mercury into the burrow, the worm being taken out on the day following the injection. One of my former students, Captain F. C. Kelly, (M.C.) U.S.A., kindly informed me several years ago that in Hong Kong the worms are caused to extrude in their entirety by keeping the ulcers covered with plain cold water dressings continuously for ten days to two weeks. Ransom states that Macfie had good results with the intravenous injection of tartar emetic, 1 gram being given every second day until a total of 6 grains had been given, but I do not know that anyone else has had this experience.

TRICHINOSIS

Trichinosis is a disease which is acquired when the encysted larvae of *Trichinella spiralis* are ingested. The larvae are liberated by the action of the digestive juices, the adult worms quickly develop in the upper part of the intestinal tract, copulation takes place, the males die, and the females burrow into the submucosal tissues whence they discharge the new crop of embryos into the lymph spaces. These embryonal forms are carried into the blood stream, which conveys them to all parts of the body, some of the embryos also undoubtedly penetrate through the tissues by their own motile power. Ultimately they come to rest in the voluntary muscles, principally of the lower extremities, where the developing larvae give rise to an inflammatory reaction and are finally walled off by connective tissue, sometimes

with calcification in addition. An individual cyst is barely perceptible to the naked eye. This process goes on in the rat, the pig and in man. The pig acquires the cyst through eating the carcass of an infested rat or other meat-eating mammal or through eating trichinous pork in raw garbage or in the offal at time of slaughter while man acquires it by eating the uncooked or insufficiently cooked flesh of the pig but just how the rat acquires it is not so clearly known. Certainly his opportunities are sufficiently great however for the larvae have been found in the flesh of twenty five different mammals this rodent is also not above eating the flesh of its own kind. That the parasite is transmitted only by the ingestion of infested flesh is practically certain for all attempts to perpetuate the disease by fecal contamination have failed.

The symptoms in man are caused by the presence of the worms in the intestinal tract by the presence of larvae in the muscles and elsewhere and through the action of toxins which are liberated by the worms themselves, and by the extensive destruction of muscle tissue. From three days to three weeks after the ingestion of trichinous pork the patient is seized with nausea vomiting intestinal cramps and usually either diarrhea or constipation and tympanites. There are also chilliness and sweating and a fever which much resembles that seen in typhoid many times a typhoid like skin eruption also appears. Edema around the eyes but often involving the whole face and the lower extremities as well is a characteristic feature of the disease as is also tenderness of the muscles near their tendinous attachments. Diplopia is sometimes complained of early in the attack. There is usually a pronounced eosinophilia beginning in the second week. The encysted larvae may be found in an unstained teased or sectioned bit of muscle tissue that has been removed under local anesthesia sometimes active embryos are demonstrable in the blood and spinal fluid. There is also now available through the work of Breiman an intradermal test which seems to be positive in all save very mild cases it appears that false positive reactions may be given by persons recently receiving quinine treatment for malaria or certain of the arsphenamines for syphilis (Augustine and Theiler, 1932). McNaught *et al* (1941) has found the newer precipitin test in almost perfect agreement with the intradermal test. Symptoms of encephalomyelitis anterior poliomyelitis, polyneuritis optic neuritis cranial nerve paralysis and meningitis have all been recorded and bronchial and pulmonary signs are present in about 56 per cent of cases. Myocarditis is one of the most serious complications, Spink (1931) felt that the histologic picture in the myocardium was not positive but Terry and Work (1940) seem to be in disagreement.

The mortality in trichinosis is usually stated to be about 5 per cent but bearing in mind that the disease is always mild in children and that many adults undoubtedly have undiagnosed slight attacks it is very probable that we can really have no true notion of the total mortality in the disease. On the other hand 10 family or neighborhood outbreaks in which large quantities of a particularly bad lot of meat have been eaten raw or nearly so the death rate has frequently been from 50 to 100 per cent. The duration of the disease in nonfatal cases in such outbreaks is very variable, an individual may completely recover in a few days or he may lie in a state much resembling that of typhoid fever for ten weeks or more. Post trichinal rheumatism is often alleged to persist for many years after recovery from the acute attack, but

none of Bercovitz's (1940) carefully studied 70 patients had residual symptoms of any sort lasting more than a year

In 1937, Magath asserted that from 10 to 20 per cent of the adult population of the United States have acquired trichinae most individuals however having had no intimation of the infestation he well makes the point that there is still need of emphasizing to all classes the importance of cooking pork thoroughly before consuming it. The review of Lewis *et al* (1940) of recent studies throughout the country indicates that Magath's figures were not too high indeed in some areas evidence of infestation at some time in life has been found in more than 30 per cent of routine autopsies. Van Someren's (1937) study of 200 diaphragms in England where the law compels the boiling of all garbage before its use in feeding hogs reveals an incidence there of only about 1 per cent just how this author justifies his statement that the general level of hygiene and habits of the British people probably plays the principal part in reducing risk of infection. I am sure I do not know. The incidence used to be very high in parts of Germany, but what it is today of course we do not know nor are there accurate figures available for most of the rest of the world

THERAPY

The specific treatment of trichinosis is in a most unsatisfactory state or perhaps one should say a negative state for the truth is that all measures have completely failed. All the vermifuges have had their advocates but none has been shown to have any consistent value bearing in mind that results in single cases are not significant in a disease whose severity and mortality are as variable as they are here. Roentgen ray and radium have failed as have also the arsphenamines, tartar emetic, the dyes and the sulfonamides. A satisfactory antiserum has not been produced, convalescent serum has not had sufficient clinical trial to enable us to adjudge its value.

In the beginning *ie* while gastro intestinal symptoms are prominent all writers are agreed that the patient should be thoroughly purged. Three grains (0.2 Gm) of calomel or 1 ounce (32 cc) of castor oil should be given to be followed in either case in four hours by $\frac{1}{2}$ to 1 ounce (16-32 Gm) of magnesium sulfate or an equivalent dose of some other saline. The parasites may live for five to seven weeks in the intestine and it is possible at least that such females as have escaped impregnation and have therefore not burrowed into the submucosa at the time of diagnosis, may be swept out of the tract by this purgation. If the case is a severe one the best symptomatic treatment is believed to be that employed in the handling of a case of typhoid fever without of course the stringent aseptic and antiseptic precautions which are necessary to prevent the spread of this latter disease.

FILARIASIS AND ONCHOCERCIASIS

Filaria (Wuchereria) bancrofti is a small worm that lives in the lymphatic glands and vessels of man. The female worms give birth to living larvae which pass their life in the blood stream, during the day they accumulate in

the lungs, the heart and the large thoracic vessels, but at night they come out into the general circulation in large numbers. If the infested individual reverses his diurnal scheme, the embryos accommodate themselves to the reversal and appear in the blood stream during that portion of the twenty-four hours in which the patient is sleeping. When infested persons are bitten by any one of a number of species of mosquitoes the larvae enter the body of the mosquito and undergo certain changes there, the metamorphosed larva being deposited upon the skin of another individual, which the mosquito bites at a later period pierces the skin and enters the lymphatics, there to grow to adulthood and send its own shower of larvae into the blood stream. It is the presence of the adult filaria in the lymphatic tissues, and the irritative changes there set up, that induces the symptoms of the disease, though secondary infection probably aggravates the condition. An attack is ushered in by a sudden rise of temperature, usually accompanied by rigidity and often by delirium and vomiting, and an acute lymphangitis of a leg or foot. There is nearly always severe headache and often dizziness, constipation and herpes labialis are frequent accompaniments. The affected part is enlarged and erythematous and the lymphatics and regional glands are swollen and tender. The symptoms disappear completely in a few days, with subsequent intense itching and desquamation, but the patient experiences many of these attacks and it is finally noticed that the swelling is not entirely subsiding in the intervals. Ultimately the attacks cease to recur but the chronic deforming enlargement, known as elephantiasis, remains. The establishment of elephantiasis seems to bring about the death of the adult worms and thus to cause the disappearance of larvae from the blood stream. Next in frequency to the legs, the scrotum is involved, elephantiasis of the arms, the penis, the scalp, the breasts, and the subcutaneous tissues have also been reported. Chyluria is usually a symptom of the disease, due to the blocking of the thoracic duct and the bursting of some of the bladder lymphatics. Large boggy swellings in the groin are frequent and filarial hydrocele and orchitis are not uncommon. Leg abscesses in filariasis patients often contain portions of dead worms. The living larvae are found in the blood and in the chylous urine and sometimes in the fluid obtained from involved glands.

Filaria loa spends its larval stage in the blood, with the diurnal periodicity of *F. bancrofti*, but wanders about in the subcutaneous tissues during its adult life. The name "Calabar swelling" has been applied to the fleeting edemas which it causes during the course of these wanderings, areas of localization in the spleen may also react with inflammation and fibrosis. The parasite sometimes crosses the eye, giving rise to conjunctivitis during its passage. A fly of the genus *Chrysops* is the vector of this form of filaria.

Filariasis occurs in the tropical belt all around the world, but the distribution of endemic centers within this belt is a very unequal one, it is not possible to mention in a work so limited as the present one, all the places where this disease has been diagnosed. Statistics as to incidence and mortality are of doubtful value since many individuals seem to be able to harbor the adult worms and the larvae without ever manifesting any symptoms. Indigenous cases in nontropical regions are very rare, though here in the United States we have an endemic focus in Charleston, S. C., and Poincexter and Jones (1934) have reported the case of an individual who had never traveled more than 100 miles distant from Washington, D. C. *Filaria loa*

disease is confined to a very small area on the West Coast of Africa, though the report of Low (1927) indicates that this entity exists much farther inland than had been previously suspected

In Guatemala and in certain southern provinces of Mexico, Strong (1931-1938) and his associates have been investigating the disease characterized by the presence of subcutaneous fibromatous nodules on the head and in many cases disturbances of the eyes and loss of vision. He has found that the tumors contain adult male and female *Onchocerca caecutiens*, and that not mosquitoes but three species of *Simulium* flies are concerned in the transmission of the disease. In some portions of tropical Africa essentially the same disease prevails, but the filarial parasite there is *O. volutus*, and the nodules occur on the body more often than on the head. Apparently in Africa there is also a reservoir of the disease in cattle and certain of the larger wild animals, notably antelopes.

THERAPY

The symptomatic treatment of early filariasis involves no especial difficulty as the attacks are of short duration though very distressing in nature. O'Connor and Hulse (1935) have confirmed in Puerto Rico what others have observed elsewhere, that the taking of a purge when the attack threatens mitigates the symptoms and lessens their duration—may, indeed, even avert the attack. Rest in bed is usually self-imposed, but resort to analgesic and sedative drugs must many times be made. The involved part is relieved by elevation and cold applications. In the lymphangitis of the cord that often accompanies filarial orchitis the pain is so great that large doses of morphine are required to give relief. Chyluria may sometimes be controlled by elevation of the pelvis and reduction of the fat in the diet.

Specific therapy has completely failed in filariasis. Hawking (1940), reviewing the subject and reporting his own experience, finds that none of the chemotherapeutic agents, including the sulfonamides, are effective, perhaps it should be noted, however, that Earle (1941) has reported some successes in treating the complicating lymphadenitis and cellulitis with sulfapyridine. Several observers have considered that in selected cases, after the inflammation of an acute attack has subsided, dissection of the thickened lymphatics will accomplish removal of the parent worm. In 1934, Golden and O'Connor were somewhat encouraged by the results of roentgen therapy applied locally over fairly large areas. Japanese observers (JAMA, 101, 1575, 1933) were also using this method of treatment at that time, but I have seen no subsequent reports in the literature. There is some evidence that a change of climate is helpful, at least Puerto Ricans come up to New York in that hope.

The treatment of elephantiasis is principally surgical, scrotal cases give the most satisfactory results, but the operative procedures so far evolved apparently still leave much to be desired. Bowesman (1938) reports that the condition is simply and safely alleviated to some extent by weekly injections into the femoral artery of 2 to 3 cc of sterile 10 per cent glycerin. Knott (1938) says that prolonged firm bandaging induces prompt symptomatic relief and effects gradual removal of the lymphedema. In filaria loa disease the parasite may be removed by simple incision when it crosses the eye; its

removal from the subcutaneous tissue is sometimes accomplished in the same manner

In onchocerciasis, the tumors (and the contained adult parasites) can be easily removed under a local anesthetic, but in some cases the microfilariae continue to circulate in the body for at least several years. Chemotherapeutic agents have failed in this disease as in filariasis

STRONGYLOIDES INFECTION

Physicians in the southern United States are becoming very familiar with this entity which has long been recognized in other subtropical as well as tropical regions. The life cycle of the causative worm *Strongyloides stercoralis* is much like that of its close relative, the hookworm, except that it embeds in the mucosa instead of lying free out in the lumen of the intestine, and with the further exception that during the time in which the larvae are migrating from the capillaries into the bronchioles an acute inflammatory reaction may take place in the lungs. Faust and DeGroat (1919) apparently feel that self infection (larvae penetrating into the circulation without having passed out of the body) is an established fact. In very light infestations there may be no symptoms, but in moderately heavily infested patients there is diarrhea with distress after meals, alternating at times with constipation. In severe cases there is intractable diarrhea, great emaciation and, occasionally, profound toxic edema. Positive diagnosis can be made only on finding the typical motile larvae in the stools, since the eggs closely resemble those of the hookworm.

THERAPY

The anthelmintic drugs have failed here since the worms are embedded in the mucosa and cannot be reached by an agent which is not absorbed.

Faust (1932) reports the treatment of about 200 cases in New Orleans with gentian violet, a method first reported by DeLangen, in Java. Two $\frac{1}{2}$ grain (0.03 Gm.) enteric-coated tablets of the medicinal dye are given by mouth to adults three times daily before meals for from seven to ten days. In a follow up examination of 47 patients all but 2 had been freed of the infection, in 4 cases, two courses of treatment were needed. Two patients reported mild nausea, but no other deleterious symptoms were observed. This treatment is said to kill the adult worms but not the larvae or the eggs. Kourf and Sellek (1936) have also reported favorably. Hinman (1938) felt that possibly the drug was of some value in the 46 cases in which he used it, Levin (1938) says that 3 or more courses of treatment with gentian violet are necessary in order to obtain a negative stool, but he seems to have accomplished this in only 10 of his 17 cases. Simpson (1930) reports that he has sometimes succeeded with the use of iodine. A saline is given in the evening and the next morning withholding breakfast, a duodenal tube is passed and the stomach is irrigated and the duodenal contents aspirated, then 4 cc. of compound solution of iodine (Lugol's solution) is introduced and the tube removed, the treatment being repeated on alternate days until the duodenal contents and stool are negative for ova, parasites and larvae.

HOOKWORM DISEASE

(Uncinariasis Ankylostomiasis)

Hookworm disease is caused by two species of intestinal worms, *Ankylostoma duodenale* and *Necator americanus*. The life cycle of these worms is very simple since man is the only host. The eggs are passed in the feces of an infested person. If the stool is deposited on the soil under suitable conditions of warmth, moisture, and shade, larvae capable of infesting man develop in five days. This infestation takes place when soil thus contaminated comes into contact with the bare feet or with other naked portions of the body. The larvae then pierce the skin and enter the circulation which carries them into the lungs, the alveolar walls of which are pierced in turn and the free air spaces entered. In the next stage the larvae pass up the trachea and larynx and then down through the esophagus and stomach into the middle portion of the small intestine, where they attach themselves and attain maturity. From six weeks to two months after the larvae have penetrated through the skin the adult female worms are laying eggs which are passed out with the feces. Individual worms live as long as seven to ten years during which time they disengage and reengage at many sites in the intestinal mucosa. Each time the head is withdrawn a point is left which bleeds for some time as the head of the worm secretes an anticoagulant substance. *A. duodenale* also passes much blood through its body but *N. americanus* does not. It has been felt in the past that these worms secrete a hemolytic toxin but as the point has never been proved the consensus is now that the anemia of hookworm infestation is due entirely to gross loss of blood as described above.

Hookworm disease prevails throughout the tropics and also in many warm but distinctly subtropical regions. It is principally a disease of native populations but Manson Balir (1949) warns that it may occur among Europeans in infested regions even though their personal habits would seem to exclude the possibility, the infestation occurring in these instances in his opinion via the mouth. Endemic foci also exist in the Witwaters Rand gold mines in the Transvaal and in the coal mines of such of the cooler portions of the globe as central Europe and the south of England. Miners contract the disease by contact of their hands, arms, knees, elbows or buttocks with feces-contaminated soil in the mines but everywhere else it is almost exclusively contracted by those who go about barefooted in regions where the first principles of decency in the matter of personal and communal hygiene do not obtain. That is to say in the tropics where poverty forces the native to go barefooted and custom permits him to defecate where he pleases, there other things being equal hookworm disease will prevail. But that very similar conditions obtain in more enlightened communities is certainly a blot upon civilization's record. Hookworm problems which vary in extent in different regions still exist over large areas in our South but the analysis of Keller *et al.* (1949) indicates that in six of the most badly infested states there has been an average decrease of 68.3 per cent in the incidence since the campaign for the control of hookworm disease by the Rockefeller Sanitary Commission (1910-1914).

Infestation of individuals begins as soon as they are old enough to range very far away from the house door and continues as long as they go about

barefooted in the endemic region. The passage of the larvae through the skin causes in most cases a local vesicopustular lesion known as "ground itch." After a variable period of time, depending upon the degree of the infestation and the individual's resistance, the symptoms begin gradually to appear. At first there are slight gastric disturbances, which disappear upon the taking of food, then the individual develops a desire for unusual articles of diet, such as clay, chalk and hair. This symptom is often denied by patients, but in some regions the craving is openly confessed and pandered to, as in mid-Java, where, according to Darling, a certain lumpy earth of volcanic origin is kept on sale in the shops. Pallor appears, there is dizziness and palpitation and breathlessness on exertion, oftentimes the pulse is erratic and sometimes there is a low grade intermittent fever, and the patient becomes mentally dull and indifferent and physically less and less suited for the more arduous forms of labor. Examination of the blood reveals a reduction in the hemoglobin which is not of proportion to the reduction in the number of erythrocytes and sometimes eosinophilin, the stools contain many hookworm eggs. If the patient is a child he is often pot bellied and much below the average in size. Thus stunted, mentally and physically weak, anemic, shiftless and indifferent, the hookworm victim goes through life an economic drag upon the region which, in his ignorance, he continues to pollute, but he seldom dies of his malady. In the tropics, however, where infestation is much heavier than in the temperate zones, death primarily due to hookworm disease is not rare, the terminal picture is said to be one of extreme anemia, physical exhaustion, anasarca and cardiac failure. Ashford *et al* (1933) performed a very great service by placing on record 7 cases acutely and massively infected from the same source, during the first week there was much discomfort from dermatitis and at the end of this period soreness in the throat and a feeling of having caught cold. Within another week great weariness and fleeting epigastric pain had appeared, which was followed by colic, great loss of weight, strength and color, and in all save one case by diarrhea, loss of blood in the stool was alarming in several cases and all became seriously anemic.

It is thought the mysterious AAA disease of the Ebers papyrus dating from the Egypt of about 1550 B.C., might have been hookworm, other intestinal worms are with certainty mentioned and prescribed for in that ancient compilation. As century followed century, from being known as Egyptian disease it came to be called tropical chlorosis, miner's anemia, and St. Gotthard tunnel disease. In 1843, Dubini described *A. duodenale*, and in 1866 Griesinger showed its causal relation to the disease. *A. americanus* was discovered by Stiles in 1902. In 1898 Looss discovered the remarkable route by which the larvae reach the intestine.

THERAPY

Extensive experience in the campaigns for control of this malady has conclusively shown that routine drugging of individuals who must remain in endemic regions is of secondary importance to the sanitary measures necessary to prevent reinfestation. Still today, however, both within and without such regions, chemical disinfection must often be resorted to. Wickramasuriya (1937), whose experience in Ceylon has apparently been vast, states unequivocally that the fear of abortion or miscarriage resulting

from the treatment of hookworm disease in pregnant women is groundless and furthermore since hookworm disease has a very deleterious influence on pregnancy, and vice versa pregnancy should be regarded as a special indication for the use of the effective anthelmintic agents. The following are the chief of these agents. Their toxicology is presented at the end of this chapter.

Tetrachlorethylene—The superiority of this drug seems to be well established upon the basis of its ease of administration, relatively low cost, low toxicity, and high efficacy in eradicating the worms in a single treatment. Smillie (1939), who has had wide field experience, speaks very highly of this drug. Brown (1934) advises that the intestinal tract be cleaned out by a magnesium sulfate purge the evening before (though this may be omitted) and the treatment be given next morning omitting breakfast. The average adult dose is 3 cc divided into 6 capsules, or the liquid may be poured onto sugar. Mapleton and Mukerji (1933-1940) and numerous others use 4 cc routinely. Immediately after taking the drug a magnesium sulfate purge is taken. Or the drug may be added to the saline and the two taken together rinsing the glass with water and swallowing the rinsings also. The patient should rest after taking the dose and may eat after purgation has occurred. If ova are found in the stools upon reexamination after two weeks the treatment may be repeated. The dosage for children is 0.2 cc for each year of age up to fifteen. The drug has a more pronounced taste than carbon tetrachloride but as pointed out by Hare and Dutta (1939) it is pleasant to smell, does not burn the mouth and produces a slight drunkenness enjoyed by coolie populations. Lambert (1933) had earlier referred to this intoxicating action but also not as an objectionable feature. Castor oil is not to be used with this drug or with carbon tetrachloride (see below) for it increases the toxicity of both.

Carbon Tetrachloride.—This drug is tasteless and very effective. In Egypt, Tomh and Helmy (1933) had only 19 deaths among 1 600 000 treated patients and they say that most of these could have been prevented. Carbon tetrachloride is given in the same dose and by the same methods as tetrachlorethylene (see above). Pregnancy is not a contraindication to the use of the drug which is probably true of tetrachlorethylene also though the fact has not been definitely established so far as I am aware.

Oil of Chenopodium—This drug is given mixed with a dose of castor oil appropriate to the patient's age, which seems definitely to lessen absorption and hence toxicity. Dosage is 1.5 to 2 cc for the adult, and the following (Darling) for children:

Age	Dose in cc
4	0.2
6	0.3
8	0.4
10	0.6
12	0.7
13-14	0.8
15-16	1.0
17-18	1.25
19-20	1.5

Oil of chenopodium is also quite effective against round worm, a matter of some importance as indicated below. It has been given in millions of

cases with only a few recorded deaths (Smillie said, in 1939, that he had had 22 deaths in over a million persons treated in Brazil) and even the number of instances of mild or moderately severe reactions is very small, nevertheless, it does have a higher toxicity than either tetrachlorethylene or carbon tetrachloride, it should not be repeated under two weeks. One should be especially cautious with it in poorly nourished individuals, in advanced cases of chronic cardiac or nephritic disease, in pregnancy, and in acute or chronic dysentery, it is considered to be contraindicated.

Combination of Oil of Chenopodium with One of the Other Anthelmintics.—Carbon tetrachloride has usually an undesirable effect upon round worms, namely, that of increasing their activity, with very serious results in some instances. The custom has now arisen of using oil of chenopodium in combination with either this drug or tetrachlorethylene when there is a mixed infestation with round- and hookworms. According to Brown (1934), the usual procedure is to give in one dose a mixture of 0.05 cc. of oil of chenopodium for each year of age up to twenty years and 0.1 cc. of tetrachlorethylene for each year of age, the adult dose being 1 cc. of oil of chenopodium plus 2 cc. of the other drug. One must be sure to follow this mixture with salts and not castor oil for the latter increases the toxicity of both tetrachlorethylene and carbon tetrachloride.

Thymol, Betanaphthol, Hexylresorcinol—Thymol, the classical drug in mass attacks upon the disease, has now been superseded by the drugs discussed above, it was no more effective and was both more toxic and more expensive—Lane (1940), practically alone among experienced men, still holds out for this drug. Betanaphthol never made much place for itself because it was both toxic and ineffective. Hexylresorcinol was reported to be highly effective in the preliminary studies of Lamson *et al.* (1932). Later, Brown (1934), of the same group, states that it requires two treatments (methods as in Round worm) with this drug to accomplish what tetrachlorethylene will do in one, but he says that unpleasant symptoms have not been complained of and that such treatment will rid the patient of both round and hookworms. Smillie (1939) feels that hexylresorcinol (for methods of usage see Round-Worm) is the best of all drugs now available but finds it too expensive for mass employment.

Iron Therapy.—There is only so much iron in the body and most of it is in the circulating hemoglobin. If the hookworm infestation has been overwhelmingly heavy, or if of only moderate degree but has persisted for a long time, the loss of circulating iron will be so great that the storage depots will have been seriously depleted by the time the patient is freed of the worms by the use of anthelmintic drugs. Under such circumstances recovery will not be rapid unless vigorous iron therapy is employed. Payne and Payne (1940), whose studies in Puerto Rico supplemented the earlier and well known work of Rhoads *et al.* (1934), showed that following anthelmintic treatment alone it required one to two years for hemoglobin values to reach a satisfactory level but that the supplementary use of iron much improved the picture—facts which have been empirically known for a long time of course in all lands with heavy hookworm infestation.

THE TOXICOLOGY OF VERMIFUGES

Aspidium—The milder symptoms consist in colic, diarrhea, headache, dizziness, dyspnea, and yellow vision. Any one or all of these symptoms are not infrequently seen in slight degree, but more serious manifestations of poisoning, such as violent muscle cramps, jaundice, evidences of renal injury, blindness, delirium, convulsions, and coma, are very unusual, death is rare.

The stomach should be emptied by the use of a nondepressing emetic, such as powdered mustard (a teaspoonful in a cup of lukewarm water), or copper sulfate (4 grains, or 0.25 Gm., in water), or zinc sulfate (15 to 30 grains or 1 to 2 Gm., in water). A full dose of magnesium sulfate, 1 to 1½ ounces (32 to 48 Gm.), should be given to flush out the bowel. The patient may be stimulated by heat, strychnine, caffeine, digitalis, etc., as indicated by the symptoms. Recovery is slow.

Pepo—The toxicology is unimportant.

Pomegranate—The toxicology is unimportant.

Pelletierine Tannate—Mild toxic symptoms, which are frequent, consist in dimness of vision, dizziness, muscle cramps, formication, weakness and trembling. Overdoses cause partial blindness with dilated pupils in addition to the above symptoms in aggravated form, there is also violent headache, vomiting and diarrhea, sometimes convulsions.

The treatment is the same as for poisoning with aspidium, but when an overdose of pelletierine has been taken one should proceed very cautiously as these patients are profoundly prostrated.

Santonin—Overdoses of this drug cause early vomiting, abdominal cramps and sometimes but not always, diarrhea. The patient is dizzy and very weak and may complain of headache and painful urination. It is said that hematuria may also occur. In severe cases there is an astonishing fall in temperature and the patient may go into violent convulsions; coma usually precedes death.

The treatment is the same as for poisoning with pelletierine. Every attempt must be made to keep the patient warm, and all available stimulants may be tried. An anesthetic carried only to a light stage of relaxation, will control the convulsions, but if the patient sinks into coma he is almost certain to die.

Yellow vision often occurs in the routine use of the drug but is of no importance if unaccompanied by other symptoms.

Thymol—Barnes, whose experience with thymol in the International Health Board campaigns was very extensive, wrote that the majority of patients treated with the drug showed some signs of its toxic action, such as flushed face, slight dizziness, and drowsiness. Very rarely more serious symptoms appeared, vomiting and gastrointestinal pain, severe vertigo, headache, tinnitus, visual disturbances, and cyanosis and collapse. There were very few reported deaths.

The treatment is the same as for poisoning with aspidium. *Alcoholic stimulants must not be used.*

Betanaphthol—Smillie described 4 cases of poisoning in 70 patients treated with large doses of this drug. The toxic action of betanaphthol in these 4 cases was a destruction of the red blood cells. The drug selected the red blood cells and destroyed them in great numbers, with resultant severe anemia, icterus, enlargement of the spleen and liver, enlargement

of the gallbladder, and hemoglobinuria. The white blood cells apparently were not destroyed by the drug. The liver, spleen, kidneys and other organs of the body were not affected primarily, but were markedly affected secondarily, because of the anemia, and because of the injurious effects produced by the elimination of large numbers of destroyed red blood cells. One of the patients had no subjective symptoms whatever, and another complained only of thirst and a slight weakness. The other two were very ill, there were nausea, vomiting and diarrhea, headache, exquisite tenderness in the regions of the spleen and gallbladder, a rise in temperature, pulse and respirations, and profound prostration. Both patients recovered.

The treatment consists in promoting elimination and providing stimulation as in the treatment of aspidium poisoning. Blood transfusion would seem to be indicated.

Oil of Chenopodium—The symptoms of chenopodium poisoning are referable to the central nervous system and consist in nausea and vomiting, dizziness, internal ear deafness, tingling of the hands and feet, muscular incoordination, and semicomatose. The kidneys are also affected as is shown by albuminuria and the appearance of casts.

The treatment is similar to that employed in combating aspidium poisoning. In laboratory experiments, Salant found digitalis especially valuable as a stimulant. To combat the renal irritation, Darling advises the administration of hypotonic salt solution by the Murphy drip.

Carbon Tetrachloride—Any one, or a combination of several of the following factors is believed to account for the rare deaths from this drug.

Alcohol—The drug is extremely toxic for chronic alcoholics and for those who drink alcohol immediately after treatment. Violent vomiting, bleeding into gastro-intestinal tract, severe jaundice after forty-eight hours, urine scanty and highly bile stained.

Round worms—The drug may so greatly stimulate ascarids that writhing masses of these worms can be seen through the abdominal wall. Pharyngeal and intestinal obstruction has been brought about in this way.

Food—If the drug is not taken on an empty stomach and if food, especially fatty food is taken too soon after taking the dose, toxicity is greatly increased. In a recent discussion, Mackie (1939) stated his belief that the diet for two or three days prior to administration of the drug should be low in meat as well as in fat.

Calcium—Lamson, Minot and Robbins have shown that the tendency of the drug to cause acute central necrosis of the liver is greatly increased by calcium lack. Since such lack is rarely seen except in poorly nourished individuals, all such patients should have their weight improved and the calcium supply restored before using carbon tetrachloride in them.

Tetrachlorethylene—No serious toxic symptoms have been reported except for 2 instances recorded by Sandground (1931) in which the patients were said to have gone into coma lasting several hours. A few patients complain of transient dizziness and giddiness.

Hexylresorcinol—No systemic reactions of a serious nature have been recorded.

Gentian Violet—The symptoms induced by this drug are principally gastro-intestinal and as recorded under Pin worm quickly subside, contraindications are given in the same article. I have seen no report of serious systemic poisoning from this drug used as an anthelmintic.

ALLERGIC DISTURBANCES

ALLERGIC DISTURBANCES

HAY FEVER

The common, or seasonal, type of hay fever is that which begins every year when the particular pollen by which it is caused begins to be wind borne, and persists until pollination ceases. The quite accurately predictable date of initiation of the annual attack, which used very often to bring down upon the heads of the victims of this disease the charge of being hysterics, is now known to be due to the fact that the flora of a given region pollinates with astonishing regularity under ordinary conditions, one should not overlook the fact, however, as emphasized by Feinberg and Durham (1935), that unusual weather conditions can affect pollen production very significantly. The pollens of the common trees, grasses and ragweeds are the most usual offenders, conferring, respectively, the titles "spring," "summer," and "fall" hay fever. The symptoms are itching and congestion of the eyes, violent paroxysms of sneezing, and a thin irritating discharge from the nose, often very profuse, oftentimes there is also itching inside the mouth and "behind the eyes." The symptoms vary a great deal in severity during the day, being usually worst in the morning. In most cases there are "good" days and "bad" days, though very many sufferers are more or less incapacitated for active participation in affairs throughout the entire "season." Some of the patients experience asthmatic attacks in conjunction with their hay fever. Those who are affected by the ragweeds can entirely escape their attack by annual migration to a region where the wind does not contain these pollens, but escape for spring and summer sufferers is to be had usually only at sea, since the offending trees and grasses are quite ubiquitous upon the land. Perennial hay fever, the so-called "vasomotor rhinitis," is characterized by the persistence throughout the year of such symptoms as have been described above. Animal danders, vegetable powders, house dust, foods, and drugs are held to be principally responsible for this type of the disease. The line between seasonal and perennial hay fever can be by no means always sharply drawn.

I believe that the earliest clear account of this disease was that of John Bostock, in London, in 1819. It is apparently primarily a malady of the temperate zones, being almost entirely absent from the moist, low-lying, torrid portions of the tropics. The American Indian is thought to be much less susceptible to the disease than the members of any other race, at least in the western world.

THERAPY

Specific Desensitization (Hyposensitization)—The practice of "desensitizing" hay fever patients by injecting them with increasing amounts of pollen extracts at short intervals during the several months preceding their annual attack was initiated by Noon, in 1911, and has since attained a considerable vogue, though the rationale of the procedure is not as yet entirely established. Expert allergists, who prepare their own extracts and are able to give their full time and attention to the diagnostic and therapeutic

study of their cases, are apparently able to effect a considerable degree of relief in two thirds to three fourths of their patients. What proportion of this fortunate majority is actually 'cured' and what proportion only much improved is somewhat open to argument, and indeed there is not a little evidence that enthusiasm runs just as rampant among the allergists as among those in the other specialties in medicine. There is abundant evidence, however, that complete cures are much more often achieved nowadays than formerly, and the sanguine belief that 100 per cent of successes will be attainable in just a few more years of accumulating experience is perhaps not now so difficult to support by convincing statistical facts as it was some time back. But it is out of the question for the general practitioner to hope for such success either now or in the future. Allergists realizing this, are justifiably contending that all the cases should be handled by them, pending the realization of this utopian desideratum. However, I shall be obliged to continue to offer in these pages a brief outline of how the thing is done with such methods and means as the general man has at his disposal.

Methods of Testing Sensitivity—(a) **SCRATCH TEST**—After cleansing with alcohol the skin is scratched with a needle without drawing blood. A small quantity of the suspected protein is lightly rubbed in, and a drop of N/10 sodium hydroxide (4 Gm NaOH to 100 cc distilled water) is added. An urticarial wheal with pseudopods and an erythematous area is considered positive.

(b) **INTRADERMAL TEST**—About 0.01 cc of a liquid extract of the suspected substance is injected intradermally; this method is probably more clear cut and reliable than the previous one but the liability to constitutional reactions is greater.

(c) **PATCH TEST**—A small area is washed and rubbed lightly with pumice stone. The suspected material either in solution or rubbed into a paste is placed on the area and covered with a small square of cellophane and held in place by adhesive plaster. The reading is after twenty-four hours or longer.

(d) **INDIRECT TESTING (PRAUSNITZ-KUSTNER TECHNIC)**—One teat cc of the patient's blood serum is injected intradermally in a normal arm and twenty-four hours later the suspected substance is injected or scratched into this site. The usual urticarial wheal is a positive reaction.

The latter two of these tests (patch and indirect) are being nowadays much employed in dermatologic practice.

Technic of Subcutaneous Desensitization—Of the "standard" method New and Nonofficial Remedies (1941) has this to say: "No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by the amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate these doses but to avoid untoward reactions a small amount (0.03 cc) of the lowest dilution intended for treatment may be injected intracutaneously. There should be no reaction or only a minimal wheal following this test."

Timing the Injections—The usual practice in administering "preseasonal" treatment is to give fifteen to twenty subcutaneous injections at intervals of

once or twice weekly, the time of the last injection to coincide approximately with the beginning of the patient's "season," or either to antedate or postdate that time by a few days. Of course the immunity conferred by these injections when successful, is only sufficient to carry the patient through his "season" in the vast majority of instances and even then only if the "season" is a short one, the whole course of treatments must be gone through with again during the next year. A very important question from the patient's standpoint is how many years he shall have to continue faithful to the routine, *i.e.*, granting that hay fever untreated will diminish as he grows older and finally cease to plague him at all, to what extent will annual desensitizations hasten the malady's end? By far the most enthusiastic answer is supplied by Walker (1936), whose presumably permanent cures were 8 per cent of those treated for only one year but 60 per cent of those treated for five years, I think that few observers are quite so sanguine.

It is now the practice of some allergists to continue the treatment throughout the season, the usual attempt being to use the maximum dose reached before the season at weekly intervals throughout the season. Apparently a few patients cannot tolerate this dosage however, developing either pronounced local swelling or delayed minor systemic reactions or they merely complain of much lassitude on the day following the injection. Cohen (1940) advises that for such patients the dose should be reduced a quarter, a third or a half.

Another form of treatment which many allergists are now favoring is known as the perennial type, *i.e.*, the persistence in the injections for as long apparently as the patient will cooperate. The interval at which these injections are given varies in different practices but I think that Vaughn (1940), and Nelson (1940), very likely express the consensus in advocating two weeks as ideal. Constitutional reactions are of course not infrequent in this type of treatment unless it is highly individualized.

When the patient does not present himself until his symptoms have begun, it appears that something can be accomplished through coseasonal treatment, *i.e.* administering just as much treatment as the patient can stand, bearing in mind that he is being assailed by air borne pollen simultaneously, usually injections are given at one or two-day intervals with greatly reduced dosage. Under such circumstances Freeman (1936), of London, sometimes resorts to "rush" treatment—*i.e.* the patient is hospitalized and eight or more pollen doses are crammed into him daily in order to get the desensitization completed in about a week. Waldhott (1937) also reported the satisfactory use of this method in selected cases. It seems to me, however, that this "rush" method is not sufficiently free of hazards to justify the general practitioner in employing it.

Currently Nateman (1941) is experimenting with a suspended pollen tannate, and Spain *et al.* (1941) with a gelatin pollen extract. Both these preparations have the apparent advantage of slow absorption and their introduction may mark a therapeutic advance of some importance.

Oral pollen desensitization is suggested from time to time but it is still the opinion of the vast majority of leading allergists that it is inferior to the injection methods, recent reports are those of Schwartz (1940), Alperstein (1940), and Feinberg *et al.* (1940).

Reactions—It is generally agreed that an urticarial reaction however

slight, is a warning sign and dictates use of the same, or perhaps even a slightly reduced dose, at the next injection. If the patient is kept under observation for about half an hour after each injection there is little to fear since prompt subcutaneous injection of epinephrine will quickly control such local or constitutional reactions as are likely to take place during that time. One should never inject pollen extract without pulling back on the syringe plunger to make sure that a vein has not been entered. Duke routinely mixes each dose of protein solution with the following and injects the whole: 0.15 cc. of a mixture of ephedrine (3 per cent) 2 parts and epinephrine (1:1000) 1 part, plus 0.3 cc. physiologic saline. With this mixture, and by controlling the dissemination of the pollen by the application of a tourniquet above the site of injection, he has greatly reduced the number and severity of reactions. Others have had a similar experience. There are three objections to the method, however: it is rather painful; the ephedrine-epinephrine mixture may make the patient quite nervous; and the frequent use of epinephrine in this way may make him less responsive to the drug when directly needed, as for the relief of an asthmatic attack. Rice (1934) has given a valuable description of his handling of a case in which a large overdose of pollen was given through mistake: (a) intense local burning called attention to the error, (b) a blood pressure cuff was quickly substituted for the tourniquet already in place and epinephrine was injected surrounding the extract site, (c) during the next hour there was itching up the arm when the tourniquet was released at intervals for a few seconds at a time and once violent hay fever symptoms necessitated the placing of a dose of epinephrine in the other arm below a second blood pressure cuff, (d) for the succeeding three hours the periods of pollen release varied from thirty seconds to one and one half minutes, each being followed by release of epinephrine, (e) complete release was safely effected four hours after the initial injection, the arm remaining sore for two days but no further constitutional symptoms occurring, (f) treatment was resumed after three days.

Non-specific Proteins—Non-specific proteins, usually peptone, are much used in certain of the European centers, but in North America the results have not been comparable with those obtainable by use of the specific pollen substances. The method is described in Asthma.

Calcium and Viosterol—In recent years it has been both affirmed and denied that there is calcium deficiency in allergy, and equally it has been stated that calcium is and is not effective in treatment. Under such circumstances one is probably best advised to give the element a very minor place among the remedial agents in hay fever.

Rappaport (1934) and his associates showed that pollen injections and viosterol treatment combined are capable of producing somewhat better results than either alone, but they employed much higher viosterol than most men would care to use. Crandall and Feinberg (1934) gave thirty drops of viosterol daily to a series of patients without effect.

Histaminase—Several investigators have long held that the release of histamine or a histamine-like substance in the body, or the abnormal response of the body to the presence of histamine, may be directly responsible for the symptoms in the various types of allergy. Therefore, when it was discovered a few years ago that the enzyme histaminase exists in the body and is capable of inactivating histamine, clinical trials of this histaminase

egan to be made in many types of allergic patients. To date, however, despite a few encouraging reports such as that of Roth and Horton (1940), who used the drug in various types of allergy with success in some instances, the majority of the reports have certainly been unfavorable; for example, Miller and Piness (1940) failed to obtain unequivocal evidence of the drugs value in their 42 cases; Frank and Harris (1940) failed completely in their 20 cases, and Keeney (1940) in his 15 cases; Knoll and Beinbauer (1940) obtained pronounced improvement in about one-third of their 101 cases but their own analysis shows that more than half their markedly improved patients were afflicted with atrophic dermatitis or acute urticaria, both of which are given to spontaneous regression and even complete involution. Decidedly, therefore, it seems to me that a clear case has not yet been made out for histaminase, but since its toxic effects are practically negligible and its methods of administration simple, further studies would seem to be desirable. Farmer (1941) is experimenting with histamine itself (see Asthma).

Histaminase is taken orally in enteric-coated tablets in average dosage of 60 to 75 mg daily.

Ephedrine, Synephrine, Propadrine.—The use of these drugs systemically in asthma and hay fever is discussed at another place.

Nitrohydrochloric Acid.—Some years ago I revived the use of nitrohydrochloric acid by mouth. Widely scattered practitioners still continue to report to me that they oftentimes obtain startlingly good results with this simple agent; of course the larger proportion of completely negative results is never reported to me. However, the following prescription and the method of using it are worth bearing in mind and trying upon occasion

Rx Nitrohydrochloric acid (not the dilute)	5ivss	18.0
Distilled water to make	3iv	120.0

The patient is directed to take 1 teaspoonful of this in $\frac{3}{4}$ glass of water, followed by another glass of water, after each meal and again upon retiring (as near midnight as possible). This is a pleasantly acid but not corrosive tasting mixture, which may be dispensed in the usual bottle with a cork stopper. The midnight dose is very important; when it is omitted the patient will almost invariably have early morning symptoms. The ingestion of the acid, even in this large dose, cannot be looked upon as in any sense dangerous, though to protect oneself against the charge twenty years later of having ruined the patient's teeth it may be advisable to have it taken through a glass tube. Another precaution should also be taken: namely, that of forbidding the use of any laxatives or purgatives not prescribed, for there is perhaps some very slight danger of calomel being converted into corrosive sublimate by the acid. The use of the remedy is begun only with the onset of the individual's hay fever season.

Potassium Chloride.—Several years ago, Bloom (1938) reported striking benefit in 29 cases of hay fever treated with this drug by mouth. Rusk *et al.* (1939), Smith and Steffensen (1940), and Parker (1940) have also reported successful treatment in a sufficient proportion of their cases of allergies of various types to keep up one's interest in the drug. But the reports of all the specialists in allergy have been almost completely unfavorable: Harley (1939); Harsh and Donovan (1940); Rubin *et al.* (1940); Miller and Piness

(1940) Spain *et al* (1940) Furstenberg and Gay (1940) Engelsber (1940)

Bloom recommended that a 3 grain (0.3 Gm) powder of potassium chloride be dissolved in a glass of water and that 3 or 4 such doses be taken daily insistence upon dilution before taking is necessary in order to avoid severe gastric irritation Parker prescribed the drug in a solution containing 3 grains to the teaspoonful which was then much diluted with water before taking he also used potassium gluconate tablets giving a dosage three times as great to compensate for the lower potassium content of this salt Bloom (1939) says that when properly given the drug only rarely produces side effects the most important being occasional aggravation of asthma which calls for immediate cessation of treatment other rare effects are diarrhea and urinary urgency

Endocrine—Although endocrine therapy is on the whole usually quite unsatisfactory it has sometimes been directly responsible for the disappearance of allergic symptoms The coincidence of one of the classical endocrinopathies is the indication for its use and not promiscuously in allergy *per se*

Surgery—Despite the allegations of those who hold out for surgery in all conditions I believe it is now the consensus among otolaryngologists that little if anything is to be hoped for from operative procedures in the treatment of hay fever

Topical Applications—The application of a cocaine solution to the mucous membranes of the nose several times during the day will give considerable relief in many cases but the remedy is absolutely contraindicated as a routine procedure for very obvious reasons Butyn or nlypin is sometimes very well substituted 1 or 2 grains to the ounce (0.06 or 0.12 to 30 cc) in solution the latter may be used in alkaline medium The use of a dilute solution of epinephrine as a nasal spray is often unsatisfactory for two reasons first it is in itself sometimes very irritating when used under these conditions and second the patient often experiences an attack of hay fever of explosive violence when coming out from under the brief influence of this drug

Duke writes as follows for an epinephrine mixture

R _x Solution epinephrine hydrochloride (1:1000)	1.0 cc.
Dilute acetate acid	0.3
Resorcin solution (5 per cent) to make	32.0
Label: Apply to conjunctiva and nasal mucosa when necessary	

Ephedrine hydrochloride or sulfate used in a 1 to 3 per cent aqueous solution is relatively free from the objectionable features of epinephrine's action and is effective for a much longer time Neosynephrin is used in 0.25 per cent solution and in many instances with good success often without disagreeable by-effects

Ionization (Iontophoresis)—The impregnation of the nasal mucosa with zinc ions through dissociation of a zinc sulfate solution by galvanic current has been revived in recent years by Franklin (1931) in England and Warwick (1934) in the United States The nasal mucosa is first cocaineized and then the nostrils are packed with gauze soaked in 2 per cent zinc sulfate solution the positive electrodes wrapped in cotton are introduced in the

center and packed in with more cotton, the negative electrode is attached to a pad soaked in saline solution and placed in the palm or against the forearm and the current is turned on gradually to reach the point which is arbitrary for the different makes of apparatus—about 10 milliamperes for 15 minutes is usual. Many variations have of course been introduced into the technique but the above are the essential steps. The discomfort during treatment arises from the metallic taste, tingling in the nose and mouth, and profuse salivation. Reaction following treatment begins in a few hours and may last several days: nasal obstruction from swelling of the turbinates, pain in the nose, headache, perhaps a violent attack of hay fever, a gelatinous membrane which is usually expelled on the third day, leaving the mucosa red and somewhat crusted but the air passages clear. Loss of the sense of smell, and severe headache, both persisting for many months, have been reported. Some individuals have complained severely of the inability to tolerate the presence of smoke after the treatment. In some cases only one such séance is given, in others two or three or more at weekly intervals. There is certainly as yet no unanimity of opinion regarding therapeutic results. Warwick reported practically 100 per cent benefit in 40 cases, most of which were hay fever, but Franklin (1930) expresses astonishment at such results since in his 600 cases he could only claim 60 per cent relief which, except on the rarest occasion, did not amount to permanent cure. Alden (1935), compiling the results of a number of observers, finds that complete relief was obtained in hay fever in 63 per cent of 416 cases. Ramirez (1936) failed completely in 50 cases of hay fever but succeeded better in a smaller series with nonspecific perennial vasomotor rhinitis. Beck and Guttman's (1936) success was also better in this latter type of case than in hay fever, but Bernheimer (1936) has had no success in either type of case. Garfin and Pearl (1936) were encouraged by their results but looked upon their report as only a preliminary one. Hurd's (1935) attitude was about the same. And so on—apparently this method of treatment is worthy of further trial but its status is as yet by no means fixed. Occasionally burns, which tend to heal very slowly, occur without the patient's awareness of the occurrence at the time of treatment. Molitor and Fernandez (1939) believe that such burns are probably caused by electrolytic changes within the tissues and not by the generation of heat or sparking between the electrode and the body.

Pollen Filters and Air Conditioning—There seems to be no doubt that hay fever sufferers are greatly, sometimes completely, relieved during their sojourn in a room which is 'air conditioned', in more severe cases some one or other of the several types of filters which will completely remove the pollen from a room may be needed. Such equipment is relatively expensive of course and usually requires considerable care to be maintained in satisfactory operation. The provision of an adequate number of pollen free rooms in hospitals, without excessive charge for their occupancy, would be a great boon to many sufferers.

Masks—Nowadays one occasionally encounters an individual on the street wearing a mask covering the mouth and nose. I know of no controlled study of the efficacy of such masks but should think it would be difficult to prevent leaks between them and the skin and that furthermore sufficient pollen might enter through the unshielded eyes to induce symptoms in some instances.

ASTHMA

The asthmatic is one who is prone to attacks of difficult breathing, the immediate cause of which has been known, since its first mention by Floyer (1648), to be spasm of the bronchial muscles plus edema of the bronchial mucous membranes. latterly, Steinberg (1932) has shown that bronchial occlusion due to mucous gland secretion is of importance also. But the fundamental cause of these spasms still remains unknown, though many of the cases rest upon an allergic basis. The attacks may last for a few minutes to several hours and are very distressing, though death from asthma *per se* is unusual—that is, if we speak only of extrinsic (allergic) asthma, for Rackemann (1949) has reported a mortality of 8 per cent in a group of 283 patients with the intrinsic type (see below). Characteristically, the patient coughs at the end of each attack and raises sputum which contains Charcot Leyden crystals and the bodies known as Curschmann's spirals. These attacks may be infrequent or they may occur every day or several times during the night over a long period. In simple uncomplicated asthma relaxation is usually complete between spasms, but most long standing cases are complicated by emphysema and chronic bronchitis and are therefore "wheezy" and somewhat distressed at all times. Unless complicated by the two diseases just mentioned pain in the chest and cyanosis are rare during attacks. Just as we had settled down comfortably in the belief that "cardiac asthma" is always a state characterized by the mere coincidental occurrence of asthma and cardiovascular disease, Craige (1941) analyzes seven asthmatic deaths and finds it not unreasonable to conclude that, at least in severe status asthmaticus, signs of right ventricular failure may sometimes appear and be due entirely to extracardiac factors. A number of observers have stated that there is a tendency toward hypoglycemia in asthma, Abrahamson (1941) points out that the concept of hyperinsulinism underlying asthma offers an explanation for the frequency of nocturnal attacks.

THERAPY

When it first became apparent that asthma could best be studied upon an allergic basis it was felt by investigators that it would ultimately become possible to desensitize and thus cure all persons suffering from the disease, however this enthusiasm has now considerably waned, and it is frankly admitted by conservative students of the subject that there is need for more than one type of therapeutic approach to the disease. As a result, it has become possible to classify the cases as "extrinsic," "intrinsic" and "miscellaneous unclassified" asthma. The extrinsic cases are those that are believed to be caused by hypersensitiveness to some foreign substance outside the body, the sufferers having asthma on exposure to, or contact with it, i. e., these are the cases of true allergic asthma. Pollens, animal danders, dusts, foods, fungi, and a great variety of other substances are the offending agents. The intrinsic group comprises cases that are believed to be due to infection in the upper or lower respiratory tract, cases that are reflexly caused by bad teeth, nose and throat pathology, constipation, cholecystitis, or other well-defined foci of infection, and cases more or less directly associated with such conditions as pregnancy, obesity, nervousness, and bad hygiene (the

latter to include such items as unwise dietary schedule, a lack of proper fresh air and exercise, insufficient intake of fluids, and continued overwork without proper rest periods) The miscellaneous unclassified cases are, of course, just what the name implies In the extrinsic group, treatment consists in attempting to find the offending substance and eliminate it from the environment, perhaps by removing an animal, such as a cat or horse, or deleting a certain type of food from the dietary, or by removing an article, such as the feather pillow or a substance met with in the occupation, or by a more radical procedure, such as a change of climate, residence or work Where these methods fail, or seem impracticable, attempt is made to desensitize by injection as in hay fever In the intrinsic group, attempt is made to remove foci of infection, to build up resistance by the employment of bacterial vaccines, and to correct the pathologic condition of mind or body which is believed to be responsible for the asthmatic state

The results attained in the treatment of asthma are extremely variable but conservative investigators of the disease are in agreement that if the achievement of absolute cure is the only indicator of the efficacy of the treatment program, a picture is presented which is tinted much too darkly to represent the whole truth, since a large number of patients can be greatly relieved though they may never be cured in the fullest sense of the term

Specific Desensitization (Hyposensitization).—When indicated, this type of therapy is instituted just as in the treatment of hay fever, it is generally conceded, however, to be less effective in asthma than in hay fever

Bacterial Vaccines—Some years ago a number of authors were able to report results with bacterial vaccines that were quite comparable with those obtained by the institution of specific desensitization The usual method was to prepare vaccines from pure cultures of organisms obtained from the thick mucus coughed up from the lungs during the breaking up of an attack In recent years there has been little in the literature regarding this method of treatment save the general statement, frequently encountered, that "bacterial vaccines are of little if any value" In 1930, however, Stevens and Crump independently studied the use of vaccines in asthmatic children and felt that some good results were obtained in these young patients Crump prepared her vaccine from material removed through the bronchoscope

Nonspecific Proteins—Some observers believe that there is a nonspecific factor of considerable importance in specific desensitization, calling to witness the fact that relief is often obtained without much alteration in the skin test Pagniez and Widal, Abram and Brissaud, Auld, Schiff, Uhrach, and others have reported the use of peptone Van Leeuwen, Maxwell, and others claimed success with tuberculin A number of observers have used injections of milk and of whole blood, Nelsoo and Porter media broth, Van Leeuwen, and Nelson and Duckworth, sulfur, autohemotherapy has had a trial All have reported more or less success but there is no lack of dissentient or at least healthily skeptical voices Ramirez, Behrman, Irons It is an extremely unfortunate thing that some of the advocates of this kind of treatment seem to have become almost fanatical about it

Peptone—Schiff prepares a 33 per cent solution in glycerin and water by rubbing Armour's peptone siccum (dry) in the mixture of the other two ingredients, warming to complete solution, and then filtering until clear

This solution may be sterilized and will keep at room temperature. Three minims is a safe initial dose, increased by 1 minim at biweekly or triweekly intervals up to 1 cc. Auld sometimes modifies the mixture as follows: to 1 ounce (30 cc) of serum, pipetted off the patient's blood drawn from the arm on the day before, is added 1.5 Gm of Armour's No. 2 peptone, 0.006 Gm agar which has been well boiled, and about 10 drops of chloroform, the mixture is incubated at 37° to 40° C for three hours and the clear fluid pipetted off for use the next day. Very slow intravenous injections of this fluid are given twice a week, beginning with about 10 minims (0.6 cc) and increasing 5 minims (0.3 cc) each injection until 45 minims (3 cc) is reached or continuing at any time with the dose which gives greatest relief. At the time of his last report to come to my attention, Urhach was giving much of his peptone by mouth.

Whole Blood—From 5 to 10 cc of blood is withdrawn from the arm vein and immediately reintroduced intramuscularly into the buttock, injections twice or oftener per week, usually not exceeding a maximum of 20 cc per dose.

Milk—Straight whole milk is poured into a 2-ounce (60 cc) rubber capped bottle, stood in a water bath up to the neck of the bottle and boiled for one hour. Initial dose of 0.5 to 1 cc is increased by 0.5 cc at triweekly intervals up to 2 or at most 3 cc, the injections are usually given subcutaneously.

Tuberculin—Old tuberculin is used in dilutions of 1 in 1,000,000, 1 in 100,000, 1 in 10,000, 1 in 1,000, and 1 in 100 (rarely). The first dose of 0.1 cc of the 1:1,000,000 is increased at weekly intervals to 0.2, 0.4 and 0.6 cc, after which the next dose is 0.1 cc of the next dilution, and so on. When the 1:1,000 dilution is reached, some men make a practice of increasing the interval to two weeks and the dose by 0.1 cc until 0.5 cc is reached, this dose is repeated monthly as long as necessary.

Broth—A standard broth such as that used in making artificial culture media is employed in dilutions and dosage much the same as tuberculin.

Sulfur—Nelson and Duckworth (1934) used colloidal sulfur in doses of 0.5 cc of 1:10,000 to 1 cc of 1:1,000.

Autohemotherapy—This procedure is described elsewhere, see Index.

Gold Sodium ThioSulfate (Sanocrysin)—The reports are by no means convincing that this drug is of value in asthma, and its use is always fraught with danger.

Histamine and Histaminase—Histamine has been used in various allergic affections for a number of years throughout the world, but there has not been agreement regarding its efficacy. In this country Thierge in 1935, made the astonishing claim of improvement in 95 per cent of his treated asthmatics. More recently Farmer (1941) has reported more conservatively on 23 patients who had either asthma of the "intrinsic" type, or vasomotor rhinitis, or both, his results were sufficiently encouraging to warrant his continuing the study. Farmer began with a subcutaneous injection of 0.00001 to 0.0001 mg (0.01 to 0.1 gamma) of histamine phosphate, giving 2 or 3 injections weekly in the beginning and increasing the dose 50 per cent each time, later the injections were spaced at five-, seven-, ten-, fourteen- and twenty-one-day intervals depending upon the patient's tolerance and the results achieved, the maximum doses not often employed were 50 to 75 gamma. The precautions to be taken

are the same as in specific desensitization, but systemic reactions have occurred very rarely

The work with histaminase is considered under Hay Fever

Calcium, Viosterol, Endocrines, Pollen Filters and Air-conditioning, Face Masks, Nitrohydrochloric Acid, Potassium Chloride—All these measures have been discussed under Hay Fever

Iodides—The use of iodides as adjuvants in the treatment of asthma seems to be of such general acceptance that recent medical literature reveals no special studies of their efficacy. The employment of sodium and potassium iodide probably finds its rationale in the well known ability of these salts to increase exudation from the respiratory mucous membranes and to liquefy mucus, which is very tenacious in many asthmatics. Many practitioners feel that the administration of small doses of potassium iodide over a long period of time definitely prolongs the interval between spasmodic attacks. The intravenous administration of 10 per cent solution of sodium iodide in doses up to 10 cc. has been tried, but it is doubtful if this is superior to the oral method except in a few patients in whom massive doses of iodides by mouth cause excessive iodism. Some patients, however, are equally intolerant to the intravenous medication, the concentration of iodides in blood and spinal fluid seems to be about the same when given by either route. The Council on Pharmacy and Chemistry (1941) holds that the intravenous injection of sodium iodide is a dangerous procedure and should not be employed except in severe paroxysms of asthma. Cleveland (1934) has reminded us that iodism may occur in asthma patients taking proprietary or patent medicines containing iodides, perhaps unknown to their attending physician.

Epinephrine (Adrenalin, Suprarenalin; Suprarenin)—It is often tersely stated that a subcutaneous injection of epinephrine will relieve any attack of asthma, but this statement, like so many categorical pronouncements, can be accepted only with certain reservations with regard to dosage and tolerance. The usual practice when attempting to relieve an attack with the drug is to give subcutaneously 0.5 cc. of 1:1000 solution, repeating after a few minutes if relief has not been obtained and tremor has not occurred. But Sterling (1940), and many other allergists are opposed to this as a dangerous practice, Sterling says that maximal therapeutic effects can be obtained with much greater safety with a dose of 0.1 to 0.15 cc. repeated at intervals of thirty minutes for 2 or 3 doses if necessary. The amount required to control subsequent attacks varies greatly with individuals but is usually less than used in the first instance. The custom nowadays is to teach patients to administer the injections themselves in the attempt to forestall attacks, such individuals can usually assure themselves a comfortable night by the injection of a few drops in the evening—in the beginning, that is, but as time goes on they nearly always require larger and larger doses. This is true drug tolerance but there is no such thing as addiction in the opium addiction sense though Lawson's admonition is worth heeding when he points out the psychic dependence upon the drug in several of his patients. Following the animal experiments of Luckhardt and Koprányi, a number of years ago, a few men reported that massage of the site of injection of epinephrine one-half to several hours later causes the typical effect to be manifested again to a diminished extent, but subsequently most observers have failed to confirm this clinical finding.

Epinephrine should be given intravenously in asthma only under circumstances of direst necessity. No advantage is gained by combining pituitrin with it. The drug is contraindicated in advanced arteriosclerosis or if there is greatly elevated blood pressure. A case of subarachnoid hemorrhage (Flexner and Schneider, 1938) and one of hemiplegia (Keeney, 1939) in individuals with normal blood pressure are on record. Further contraindications are hyperthyroidism, cardiac dilatation, and coronary disease, pregnancy *per se* does not contraindicate the use of the drug.

Duke finds that 15 minims (1 cc) of the drug in a half glass of water by mouth is sometimes as effective as a small dose by needle, but few observers agree with him, one would think the water would have to be held in the mouth to permit sublingual absorption. Rackemann states that in the treatment of children especially, dry epinephrine (15 mg) placed under the tongue is frequently efficacious. As a result of the studies of Graeser and Rowe (1935-1939) the use of epinephrine by inhalation with absorption occurring in the lungs has become popular as a means of enabling the patient to self administer the drug. Motor-driven nebulizers are available but the more usual practice is merely to employ a glass atomizer with a hand bulb selecting carefully one capable of delivering a fine "nebulized" spray. The Council accepted 1:100 solution (specially prepared for this purpose and under no circumstances to be used for injection) is employed. Dosage must of course be determined by each patient; great caution must be enjoined in the beginning for a few extra squeezes of the bulb may induce very disagreeable if not dangerous symptoms of excessive epinephrine action. Richards *et al* (1940) are pleased with their modification of this method, in which the hand bulb is replaced by a stream of oxygen from a tank at a flow rate of 4 to 7 liters per minute. 1 cc of solution is vaporized in three to ten minutes.

In studies since 1938, Keeney has introduced "slow epinephrine." The Council accepted (1941) preparation is a suspension of epinephrine base in vegetable oil, 1:500. The advantage of this preparation apparently amply proved by experience (though Bacon *et al* [1941] notably dissent), is that the action of the drug is prolonged and therefore injections do not have to be made so frequently. Usually recommended dosage is 1 cc though the Council states the dosage as 0.2 to 1.5 cc. Insley and Segaloff (1940) feel that initial adult dosage should never exceed 0.5 cc. Of course the contraindications and reactions of ordinary epinephrine apply to this preparation, unusual reactions have been reported also in a few instances (Murphy and Jones, 1939; Cohn, 1939; Dorwart, 1940) headache, nausea, vomiting, cyanosis, dyspnea, chills, perspiration, insomnia, extreme tremor, nervousness, vesicular urticaria, swelling and edema of the forearm. In most cases these symptoms have manifestly been due to merely excessively rapid absorption of epinephrine, but it is not certain that the peanut oil in which the drug is suspended may not rarely cause an allergic reaction of its own. All who have experience with this preparation counsel that it is to be given intramuscularly and not subcutaneously, one should be certain of not being in a blood vessel before injecting. Dorwart's experience in which he was able to control the reaction to a great extent through the emergency application of a tourniquet to the arm and releasing only a few moments at a time, indicates the advisability of always injecting this preparation into the deltoid muscle and not into the buttock. In the beginning it was considered necessary to use only a dry sterilized

syringe to prevent injecting oxidizing water into the stock bottle of the mixture, but now that single-dose commercial ampules are available Keeney feels it unnecessary to observe this precaution

Spain *et al* (1939) have introduced a 1 : 500 epinephrine gelatin mixture for which they claim effectiveness comparable to the above oil mixture and the additional advantage of nonantigenicity Kalmon (1940) made a comparative study of the two mixtures on 22 patients with a total of 225 injections. In the end he preferred the oil mixture because it is less painful and irritating and gives a few hours' longer relief, the patients without exception preferred this mixture also. The gelatin mixture must be kept in the refrigerator, while the oil mixture need not be.

Ephedrine—In the treatment of asthma, ephedrine has certainly been shown by Althausen and Schumacher, Piness and Miller, Munns and Aldrich, Middleton and Chen Thomas, and many others, to be (a) very much less reliable than epinephrine in either relieving or preventing the attacks (b) when given by mouth, much slower (ten to thirty minutes) in exerting its effect than the older drug, (c) much longer lasting (often many hours) in its effects when they are obtained, (d) much more toxic. In severe cases it is usually very little if at all effective, and in moderately severe or mild cases the result seems to depend upon whether or not the patient happens to be susceptible to the drug's action, whereas practically all persons respond favorably to epinephrine. The chief advantage of ephedrine is of course the fact that it may be given by mouth. The average dose is perhaps 25 to 55 mg, but it varies widely, some patients are able to prevent an attack by taking a small dose upon retiring, whereas many others are forced to take 50 to 100 mg or more at intervals of several hours throughout the day in order to obtain any measure of relief. Both the sulfate and hydrochloride (the asserted superiority of this salt is largely academic) are available commercially in a wide range of tablets, capsules, solutions, elixirs, syrups, etc., and ampules for hypodermic administration. In Munns and Aldrich's experience with children, the minimum and maximum doses were 12 and 50 mg, respectively.

Many physicians have noted that the drug often becomes less and less effective with succeeding doses, but habit formation or abstinence symptoms have never been reported to my knowledge. The chief objection to ephedrine is the frequency and oftentimes marked though not serious nature of its side actions, which preclude its use altogether in a large proportion of patients: nausea, vomiting, sweating, bladder irritability, urinary retention, skin eruptions, dysmenorrhea, palpitation, vertigo, tremor, general nervousness and apprehension, insomnia, etc. Caffeine and nicotine in most instances definitely increase the severity of the symptoms. The greatest possible care should be exercised to avoid giving epinephrine and ephedrine in a way which might permit their effects to overlap. The barbiturates, especially amytal, are much used to counteract the ephedrine side actions. Pseudo-ephedrine (the dextrorotatory alkaloid, ephedrine being levorotatory) has had a trial in England and is now commercially available in the United States; it does not seem to have any distinct advantages over the older drug (Christopherson and Broadbent, 1934, Bray and Wits, 1934).

Many observers have reported the successful use of ephedrine by mouth in hay fever, subject to the same qualifications as to dosage and undesirable

side-effects that apply in asthma Thommen's series comprized 245 patients more than 70 per cent of whom obtained some measure of relief, 22 per cent could not use the drug at all because of its untoward effects

Benzedrine, Propadrine, Neosynephrin—Swineford (1938) found that benzedrine inhalation was useful in the relief of mild and moderately severe asthmatic attacks, and that when used in conjunction with epinephrine or ephedrine it seemed to increase their efficacy, there were a few minor toxic reactions but it seems amazing that sleeplessness was complained of following only 2 of the 69 attacks in which the drug was used

Boyer (1938) was pleased with the relief obtained in all but 2 of the 44 patients to whom he gave propadrine hydrochloride at intervals of two hours or longer, the Council (1941) advises a dose of $\frac{1}{2}$ grain (0.025 Gm.) but Boyer found it necessary to double this dose in many instances and was particularly struck with the absence of side effects as compared with ephedrine

As an inhalant, Graeser (1939) found neosynephrin in 5 per cent solution of no value, but Richards *et al* (1940), with their technic (see Epinephrine above), found it somewhat effective and free from side effects

Theophylline—Efron, in 1936, stated that one could terminate asthmatic attacks of great severity by the intravenous administration of theophylline ethylenediamine (aminophylline), he cautioned that a single drop under the skin may cause excruciating pain and also that the drug tends to sclerose veins Since Efron's report there have been several others, all favorable (Hermann and Aynesworth 1937, Brown 1938, Carr, 1940) The drug is usually given in a dosage of 0.24 to 0.48 Gm., the amount of the solution injected depending upon which of the commercially available ampules is being used Occasionally there are reactions characterized by hyperpnea, a feeling of warmth and burning of the eyes metallic taste, and nausea and vomiting Tuft (1936) found aminophylline of some value in similar attacks when given by mouth in combination with theobromine and caffeine Brown (1940) uses a capsule containing $\frac{1}{2}$ grain (0.03 Gm.) ephedrine sulfate $\frac{1}{2}$ grain (0.03 Gm.) sodium phenobarbital, and 3 grains (0.2 Gm.) theophylline sodium acetate Lamson and Bacon (1941) are studying theophylline mono-ethanolamine

Atropine—I quote Duke "Drugs of the atropine series are time honored remedies in the treatment of asthma Atropine is effective in some cases even when given in small doses In others it is ineffective It can be used either locally or subcutaneously or by inhalation If given by mouth or subcutaneously it should be pushed to the point of causing dryness of the mouth It is rarely advisable to push the drug to the point of blurring vision Some patients can tolerate 1/100 grain two or three times daily, while others who are more susceptible cannot tolerate this amount Atropine can frequently be used to advantage in conjunction with adrenalin Often the appropriate use of atropine in small doses marks the difference between success and failure in the relief of patients who have been treated according to other principles A patient nearly relieved by other means may often be completely relieved with the help of atropine"

As compared with epinephrine, atropine when used alone is the less valuable drug for two reasons first, because most patients are not markedly relieved until doses large enough to cause flushing considerable dryness of mucous membranes and more or less cerebral excitement are used, and

second, because the majority of patients become tolerant to it much sooner than they do to epinephrine

Morphine—Because of the chronic nature of the disease this drug obviously cannot be used to relieve each of the severe attacks though it will often do so effectively. As a matter of fact, most leading allergists now consider even a single dose of the drug taboo under any circumstances, the reason being that morphine causes constriction of the bronchioles, diminution in tracheal ciliary movement, and depression of the respiratory center; these actions have undoubtedly caused death in numerous asthmatic patients.

Anesthetics—Maytum (1931) relieved extremely severe attacks and Kahn (1935-1937) interrupted status asthmaticus, by the colonic administration of ether. Kahn, using equal parts of ether and olive oil, allows twenty minutes for the administration of 5 to 7 ounces (150 to 210 cc) of the mixture to the average adult, no preliminary cleansing enema is given. For a child of five to nine years he gives 1½ to 2 ounces (45 to 60 cc). Fuchs (1937) using avertin fluid found a dose of 60 mg usually adequate to induce relief, he states that once the crisis was overcome, some of his patients were free from symptoms for days and even weeks and he also considers it noteworthy that refractoriness to epinephrine was lost.

Inhalants—In mild cases the inhalation of the smoke from an ignited mixture of stramonium and a nitrate may be resorted to with advantage once or several times during the night, there is available a number of commercial asthma powders and cigarettes but the following is more economical

Rj Sodium nitrate	3ss	15 0
Powdered anise	3ss	15 0
Stramonium	ʒi	30 0
Label A teaspoonful to be ignited and the smoke inhaled		

Lippard (1939) is very skeptical of the value of these inhalants and thinks that perhaps patients are sometimes made worse by them. Steaming preparations, as described in *Common Cold* are also sometimes used.

Acetylsalicylic-acid Whiskey—Five to 10 grains (0.3-0.6 Gm) of aspirin administered together with a hot toddy, is a potent mixture which will often times conquer even severe paroxysms (Duke 1928). The first dose of the aspirin should be very small however, because many asthmatics are hypersensitive (i.e., have an allergic reaction) to the drug indeed most allergists show signs of distress at the mere mention of aspirin.

Physiotherapy and Breathing Exercises—Various forms of hydrotherapy, baths, spa cures, ultraviolet and roentgen ray exposures etc. have been advocated from time to time, but none merit special description here. In hay fever, diathermy is sometimes applied locally to the nasal mucosa, or special quartz rods are used to carry ultraviolet rays to the anterior and posterior nares. Perhaps the best known of the several schemes for inducing forced expiration is that of Hofbauer, in Vienna. The thing seemed very complicated when I saw him demonstrate it, but this may be only the statement of a fact about myself, Livingstone and Gillespie were investigating the matter in England, in 1935 but I do not know what conclusions they have reached.

Helium Inhalation—Barach (1936) made a very novel and excellent contribution in the introduction of a helium-oxygen mixture in the treatment

of patients in status asthmaticus and in those who, though perhaps not yet in extremis have become so insensitive to the action of epinephrine as hardly to respond to the drug at all. His argument was that the dyspnea in these cases is not due to oxygen want, or to the presence of carbon dioxide in excessive quantity but to the fact that in the presence of plugged bronchi the muscles of respiration are exhausted to the point of impending cessation of activity in their effort to maintain the normal velocity of air movement demanded by the mechanism which reflexly controls the respiratory activities. His proposal of helium as a new therapeutic gas was based on the conception that its decreased specific gravity in relation to nitrogen (it is only one seventh as heavy) would make a helium-oxygen mixture easier to breathe than a comparable nitrogen-oxygen mixture such as occurs in air. When put to the test the idea was soon proved to be correct, for patients were not only quickly brought out of their serious condition but they also regained in considerable measure their ability to obtain the usual relief from epinephrine. Barach (1938) reported moderate or marked improvement in about 90 per cent of 44 patients during 54 hospital admissions. The mixture (helium 80 per cent, oxygen 20 per cent) has since been successfully used by Maytum (1938), Boothby *et al.* (1939), Metz *et al.* (1939), and others.

Special Diets—Of course the whole gamut of dietary experiments has been run in this disease but the most rational would seem to be the ketogenic regimen as tried out by Peshkin and Fineman (for methods of inducing ketosis see Index). Montagnini (1934) reported success in accomplishing the disappearance of crises and initiation of general improvement in all of his small series of cases. On the other hand it is not difficult to see how dextrose feeding may also succeed since the liver, which functions best when well supplied with sugar is known to play a large part in antigen antibody reactions. Moll's (1932) success with liver diet, as used in pernicious anemia is worthy of note.

Dextrose Intravenously—Wilson recommended the intravenous administration of dextrose solution in intractable cases, in 1935 since which time the measure has been much employed in recognition of the considerable likelihood of the patient to be severely dehydrated after two or three days in which he has been unable to swallow.

Fever Therapy—All practitioners of wide experience know that a bout of fever often entirely relieves allergic maladies for the time being and in some instances even for a long period following recovery from the intercurrent acute infectious process. Latterly a number of attempts have been made to accomplish the same thing by fever artificially induced as in the treatment of neurosyphilis but the results so far have not shown this type of therapeutic approach to be as strikingly and consistently effective as one would desire from therapy as radical as this. Hyde's (1940) report is the latest I have seen.

Iodized Oil Insufflation—During the decade just ending trial has been made of the introduction of iodized oil into the tracheobronchial tree in the effort to force out bronchial plugs and purulent material. The first reports showed some degree of success but it quickly became apparent that the treatment needed to be highly individualized and was to be looked upon as more or less 'last resort' therapy. In 1937, Cripp and Hampsey obtained opinions from 64 physicians who had treated 267 cases—and there was

certainly very little enthusiastic support of the method to be had from them Crip's (1939) own conclusion from his 79 treated cases was that some temporary improvement may be expected in about 15 per cent of cases of intractable asthma Baldwin (1939) amplified his statement that the treatment is fast losing ground by saying that the more he saw of it the more impressed he was with its dangers, namely localized lipoid pneumonia and the chronic irritation and infection established about the point where the oil remains in the bronchial tree

Operative Procedures—On the Continent, Gohell reported, in 1933, that he had been practicing double sympathectomy and vagus section for a number of years In England, Levin (1935) preferred neurolysis by absolute alcohol injections and reported that complete relief was obtained in three fourths of the 23 cases which he treated in this way In New York, Stern (1937) also used this method In Baltimore, Rienhoff and Gay (1938) employed bilateral resection of the posterior pulmonary plexus Of course none of these surgical procedures is resorted to in any save the most intractable cases One would think that certainly all other possible measures would have to be exhausted before resorting to such radical procedures

ANGIONEUROTIC EDEMA AND URTICARIA

Urticaria, or "hives," is characterized by the sudden appearance in the skin of a firm, elevated, whitish patch, which is surrounded by a pink zone and is accompanied by intense itching or stinging sensations The lesion may be single or multiple and usually resembles in size the wheal caused by the ordinary mosquito bite, in the cases known as 'giant urticaria, however, the individual lesions are much larger than this and several often coalesce to form a relatively enormous patch, while in infants and young children urticaria frequently assumes a papular, vesicular, or bullous form The wheals disappear in a few minutes to hours or, in the more severe cases, may persist for several days or even weeks It is usual for hives to appear in crops with relatively long asymptomatic periods between, but some individuals are rarely free from these distressing lesions for more than a few days in succession In angioneurotic edema the subcutaneous tissues as well as the skin participate in the transient swelling, which usually affects the forehead, eyelids or lips, and is only rarely accompanied by pronounced subjective symptoms, when the internal organs are involved also, as is very occasionally the case, the symptoms may of course simulate almost anything All the recorded fatalities have been due to sudden edema of the larynx

THERAPY

It is unfortunately still the tendency of many physicians to approach these cases, especially the urticarial ones, largely from the dermatologic standpoint This is decidedly wrong because the entities are certainly allergic manifestations and the only hope of alleviating the symptoms lies in making

a thorough allergic study of each individual patient by the same methods which would be employed in hay fever or asthma. It is undeniably true that the result of such examinations will be negative in a very large proportion of cases but nevertheless in the present state of our knowledge there is nothing else to do. Plenty of positive skin reactions will be found but these usually only serve to demonstrate the antigens toward which the individual is sensitive in addition to the elusive one or more which are responsible for his hives. Still, many patients know from experience that certain foods will bring on an attack, and the approach to the problem in these patients through the elimination diets as discussed in Food Allergy, will sometimes reveal one or more additional articles of diet that are causative. Other patients who have not suspected a dietary factor themselves are occasionally properly placed in this way also. Then there are the cases an increasing number in the literature due to physical or drug allergy. To repeat the whole allergic gamut must be run and the detection of an intrinsic or extrinsic etiologic factor will be the great though rare reward.

A few special things might possibly merit mention. Menagh found biliary tract drainage effective in relieving some cases other types of focal infection have rather frequently been associated in the causative role with urticaria. Some patients are almost at once relieved by brisk saline catharsis but they are certainly in the minority perhaps it is only those whose symptoms are due to food allergy who obtain this relief. The administration of dilute hydrochloric acid as in achlorhydria or just the opposite alkaline therapy is sometimes helpful the latter is supplied by taking 20 to 30 grains of citric acid in a glass of water with each meal or in the following simple prescription:

R Potassium citrate	℥j	30 0
Syrup of orange	℥ij	60 0
Water to make	℥iv	120 0
Label 1 teaspoonful after meals and upon retiring		

Of course the vitamins have had full play. Vaughan (1940) says he has occasionally seen the intravenous administration of 30 grains (2 Gm.) of methionine succeed when all factors of suggestion could be eliminated (one might slowly inject 5 cc. of a 40 per cent solution sterilized by boiling). Histamine and also histaminase (see Asthma for methods) have been used successfully in a few instances but Laymon and Cumming (1939) were unable to draw any conclusions regarding the efficacy of the latter agent in their small series of cases. The calcium salts are often used but there is little evidence of their efficacy. Cornbleet (1935) said that the analgesic drugs act as systemic antipruritics a rather wishful terminology it seems to me phenyl salicylate 5 grains (0.3 Gm.) in capsules 2 of which are taken at meals and at bedtime acetanilid 3 grains (0.2 Gm.) every two to four hours as required. Epinephrine (see Asthma for methods) usually gives considerable relief during the attack.

For local application nothing perhaps gives so great relief as pink lotion (see Index). Fantus recommended the application of any one of the following solutions applied as hot as can be borne and followed without drying by dusting with talcum sodium bicarbonate 1 to 5 per cent, sodium carbonate $\frac{1}{2}$ to 3 per cent borax 1 to 4 per cent. According to Cornbleet an acid lotion is sometimes more effective 1 part of vinegar to 2 parts of water or alcohol. Before resorting to the alkaline bath (1 teaspoonful of sodium bicar-

bonate to the tub), or the acid bath (1 or 2 cups of vinegar to the tub), or the colloid bath (see Index), all of which may be antipruritic, it is well to make sure that the patient is not of the type of physical allergic whose symptoms are aggravated by warming the body. Marchionini and Korth (1934), on the other hand found sweat baths helpful in some of their cases.

FOOD ALLERGY

It is not possible in a single small volume of this nature to describe the host of ailments which investigators nowadays recognize as being in all probability allergic manifestations to specific food substances. Chief among them, however, are many cases of the following migraine, hay fever, asthma, eczema, several other dermatoses, gastro intestinal disturbances which may simulate any of the well known acute or chronic syndromes, some cases of urticaria and angioneurotic edema and one may add many other ailments whose allergic nature is oftentimes not suspected until demonstrated through proved hypersensitivity to a food substance.

THERAPY

Roentgen Study.—Squier (1949) makes the point very positively that a gastro intestinal examination by a competent roentgenologist to rule out as nearly as possible organic disease, is an indispensable first step if one is dealing with suspected gastro intestinal allergy.

Leukopenic Index.—Specific desensitization usually fails in these cases; indeed, skin reactions to the offending food are not always positive nor to be relied upon. A few years ago Vaughan offered a new means of detecting the food which causes the symptoms through the serial performance of white blood counts, the so called "leukopenic index." The test as run today usually consists in having the patient report at 9:00 A.M. in a fasting state of at least twelve hours' duration. After thirty minutes' rest two fasting counts are made at ten minute intervals, then during about five minutes the patient eats an average portion of the food to be tested, and subsequent counts are made at fifteen or twenty minute intervals for one hour, the patient sitting quietly without talking or smoking during this time. The food is heated to body temperature but is eaten without condiments, except in intractable allergies the food is eaten for several days before the test. If any of the counts after eating falls more than 1000 below the mean of the two fasting counts the index is considered positive; if the fall is less than this but maintained throughout the three counts it is considered "probably" positive. It is said that there may be delayed positives which will not appear within the arbitrary test period and that in case of doubt the period should be prolonged to two, three, or even four hours. The reliability of the leukopenic index has been questioned by the thorough studies of Loveless *et al.* (1938) and Brown and Wadsworth (1938), but upon the other hand, Hanson (1941), studying the method exhaustively upon himself, found it of diagnostic value. Obviously at best it is still in the experimental stage. Squier and Madison

find that an eosinophil increase occurs as regularly as does a total leukocyte reduction, and they recommend simultaneous counting of eosinophils and leukocytes to increase the accuracy of the index. Of course the value of such a test as this, should its usefulness be generally confirmed, would lie in the fact that through it the offending food substance might possibly be more easily detected than through the employment of elimination diets.

Elimination Diets.—Rowe has exhaustively exploited the possibilities of this type of treatment. After eliminating at the beginning such foods as the patient definitely dislikes or knows to disagree with him, further study of the case is based upon the use of "elimination" diets (Table 8), coo-

TABLE 8.—ELIMINATION DIETS FOR THE TREATMENT OF FOOD ALLERGY (ROWE)

Diet 1	Diet 2	Diet 3	Diet 4.
Rice Tapioca	Corn Rye	Tapioca White and sweet potato	Milk*
Rice biscuit Rice bread	Corn pone Corn rye muffin Rye bread Rye crisp	Lima bean potato bread Soya bean lima bean bread	
Lettuce Spinach Carrot Beet Artichoke	Tomato Squash Asparagus Peas String beans	Beets Carrots Lima beans String beans Tomato	
Lamb	Chicken Bacon	Beef Bacon	
Lemon Grapefruit Pears	Pineapple Peaches Apricot Prunes	Lemon Grapefruit Peaches Apricot	
Cane sugar Wesson oil Olive oil Salt Gelatin Syrup made of maple sugar or cane sugar, or cane sugar flavored with mapleline or maple sugar Olives Pear butter	Cane sugar Mazola oil Wesson oil Salt Karo corn syrup Gelatin	Cane sugar Olive oil Wesson oil Gelatin Salt Olives Maple syrup or syrup made with cane sugar flavored with maple	

* Milk should be taken up to 2 or 3 quarts a day. Tapioca cooked with milk and milk sugar also may be taken.

Note: Wesson (cotton seed) oil is included in all diets. With allergy to cotton seed as shown by skin test or history this must be excluded and a cotton seed oil shortening such as Crisco must not be used. If allergy to cane sugar is suspected, beet sugar or corn glucose may be used.

sisting of foods which experience has shown rarely cause symptoms. Rowe says that Diets 1 and 2 may be prescribed separately or together, modifying

them by substituting similar foods for any in the diets to which skin reactions or known idiosyncrasies exist. If sensitization to cereals as a group is suspected, Diet 3 may be used initially. Diet 4 may be used if the patient does not give any indications of milk sensitization, other foods being gradually added and the effect of each watched. On whatever diet is chosen, the patient should be encouraged to eat enough to prevent loss of weight, the physician substituting similar foods for any causing disturbance. If symptoms are relieved, one or two vegetables or fruits may be added the second week, and during succeeding weeks the other foods, always eliminating any which cause recurrence of symptoms, wheat, eggs and milk should be added last and their effect carefully scrutinized. Soy bean milk (Sobee) is sometimes used as a substitute in patients sensitive to cow's milk. Cemac contains beef and vegetables.

With full cooperation, it is said that patients can usually be got up to satisfying and nutritionally correct diets in a few weeks, but sometimes the process requires months or even years. That it is often extremely difficult to maintain nutrition in patients sensitive to many things has recently been emphasized by Alvarez (1939), who states also that foreign foods not often eaten by native Americans can frequently be profitably employed. It is my feeling that sufficient stress has not been laid upon the possibility of vitamin deficiencies arising during the course of elimination dieting, these patients, it seems to me, should be given synthetic nicotinic acid, riboflavin and thiamine (see Index for methods). In the hands of Rowe the results are excellent in a wide variety of allergic disturbances, though the psychic effects of "dieting" must not be overlooked. This is a type of specific therapy which, because of its freedom from dangers, its relative simplicity, and its inexpensiveness, deserves a wider trial than it has perhaps been given—if only patients were not so prone to snatch forbidden foods!

Desensitization by Mouth *Peptone Method*—Both the French and English schools had for some time been using peptones by mouth in cases of food allergy with indifferent results, when Luthlen, in 1926, showed that the fault probably lay in the use of preparations that were not truly specific. Urbach, who very actively carried on the investigations in Vienna before coming to this country, demonstrated that the treatment is worthless unless the exact peptone toward which the patient is sensitive is employed, for example, if an individual cannot eat chicken, the peptone to be used must be made from the flesh of the chicken, and if eggs are the offenders the peptone must come from the white of eggs. Small doses of these specific peptones are then given by mouth before each meal in which the offending foods are to be included (these foods having been determined by an elimination diet regime much like Rowe's, see above), in the belief that not only can the individual attack be thus prevented but that desensitization will also take place in time. The ingestion of the peptone must occur exactly three-quarters to one hour before the meal and a considerable time after digestion of the last meal has ceased, it is therefore necessary to forbid all between meals eating, which means of course that cooperation is difficult to obtain in children and that the method is hardly practicable in frequently fed infants.

This type of desensitization has not caught on at all in the United States.

Protein Dilution Method—This, the American variant of the above

method, as devised by Keston, Waters and Hopkins (1935), I am presenting here because its simplicity and inexpensiveness seem to warrant it being given a trial by general practitioners. The proposers of the method, and more recently Edwards (1940), have reported its successful employment in small series of cases and there are numerous physicians with single case successes; specialists in allergic diseases are notably reticent in the matter. The method consists in attempting to desensitize patients, in whom sensitization has been proved by elimination diets or other tests, through feeding by mouth gradually increased amounts of the convicted protein in the natural form in which it occurs in the offending foods. The chart (Table 9)

TABLE 9—PROTEIN DILUTION METHOD OF DESENSITIZATION IN FOOD ALLERGY
(KESTON, WATERS AND HOPKINS)

Directions—Beat an egg so that yolk and white are well mixed, then add the prescribed amount of egg to ordinary water and mix well. Take 1 teaspoonful of the solution once a day unless otherwise directed. Throw away the rest of the solution. Make up a fresh solution every day. Use a dilution of the same strength every day for four days.

Mix $\frac{1}{4}$ teaspoonful egg with 2	quarts of water	Take $\frac{1}{4}$ teaspoonful
Mix $\frac{1}{2}$ teaspoonful egg with 3	pints of water	Take $\frac{1}{2}$ teaspoonful
Mix $\frac{1}{2}$ teaspoonful egg with 2	quarts of water	Take $\frac{1}{2}$ teaspoonful
Mix $\frac{1}{2}$ teaspoonful egg with 3	pints of water	Take $\frac{1}{2}$ teaspoonful
Mix $\frac{1}{2}$ teaspoonful egg with 2	quarts of water	Take 1 teaspoonful
Mix $\frac{1}{2}$ teaspoonful egg with 3	pints of water	
Mix $\frac{1}{2}$ teaspoonful egg with 2	quarts of water	
Mix $\frac{1}{2}$ teaspoonful egg with 3	pints of water	
Mix 1 teaspoonful egg with 2	quarts of water	
Mix 1 teaspoonful egg with 3	pints of water	
Mix 1 teaspoonful egg with 1	quart of water	
Mix 2 teaspoonfuls egg with 3	pints of water	
Mix 1 teaspoonful egg with 1	pint of water	
Mix 2 teaspoonfuls egg with 1½	pints of water	
Mix 1 teaspoonful egg with 1	cup of water	
Mix 2 teaspoonfuls egg with 1½	cups of water	
Mix 1 teaspoonful egg with ½	cup of water	
Mix 2 teaspoonfuls egg with ¾	cup of water	
Mix 1 teaspoonful egg with ¼	cup of water	
Mix 1 teaspoonful egg with 3	tablespoonfuls of water	
Mix 1 teaspoonful egg with 2	tablespoonfuls of water	
Mix 2 teaspoonfuls egg with 3	tablespoonfuls of water	
Mix 1 teaspoonful egg with 1	tablespoonful of water	
Mix 4 teaspoonfuls egg with 3	tablespoonfuls of water	
Mix 2 teaspoonfuls egg with 1	tablespoonful of water	
Take 1	teaspoonful of raw egg	
Take 1½	teaspoonfuls of raw egg	
Take 2	teaspoonfuls of cooked egg	
Take 3	teaspoonfuls of cooked egg	
Take 4	teaspoonfuls of cooked egg	
Take ½	cooked egg	
Take ¼	cooked egg	
Take a whole	egg	
After this eat at least 1 egg every few days		

indicates the procedure in instances of sensitization to egg only. Keston *et al* offer slight variations in dilutions in connection with the other foodstuffs they have successfully used, but since they found greater difficulty in desensitizing patients allergic to egg than those sensitive to other substances,

I imagine the substitution of any other food in equal quantity for the amounts of egg shown in the chart would err only on the side of conservatism. It must be understood by one who would try this method that during its use the patient must absolutely take no foods in which even the very minutest amount of the offending substance could possibly be present, to insure such complete absence of the substance from the diet is in itself a matter of no little difficulty.

Pancreatic Enzyme Method—Oelgoetz *et al* (1935) believe that food allergy may be caused by a decrease in the concentration of serum enzymes with the result that whole proteins reach the body cells, where they may exert an irritant action. They attempt to compensate for this alleged deficiency by giving the patient by mouth a 50 per cent glycerin extract of the whole fresh pancreas, giving an amount after each meal equivalent to 5 grains (0.3 Gm) of an active dry powder. Bradley and Belfer (1939) find much that is unsound in the theoretical basis of this work, but they do not deny that a slow cleavage of protein in the digestive tract may increase the chances of absorption of antigenic molecules into the blood stream. And so the matter stands at present.

SERUM DISEASE

Serum disease is an allergic reaction caused by the parenteral introduction, by whatever route, of foreign serum. The usual symptoms are a mixture of urticaria and erythema, fever, arthritis without pronounced objective changes in the joints, swollen and tender lymph nodes, and edema of various portions of the body accompanied by urinary evidences of temporarily impaired renal function. In some instances reactions in the internal organs may give rise to symptoms which will be very confusing if the fact of serum disease is not kept in mind. In a very small proportion of cases (Bennett, 1939), usually following the introduction of tetanus antitoxin, severe neuritis occurs. The time elapsing between the giving of the serum and the appearance of the disease is usually seven to twelve days, in most cases the symptoms disappear in four to six days, but occasionally they persist for as long as two weeks. Recovery is the rule, though relapses are not uncommon.

THERAPY

Serum sickness cannot be prevented nor can it be very satisfactorily treated by any routine methods devised to date. Epinephrine (see Asthma for methods) is oftentimes temporarily effective in relieving the itching, but it must be frequently repeated, for local treatment of the urticaria, see Angioneurotic Edema and Urticaria. The arthritis does not respond to salicylates. Calcium salts have been advocated on and off through the years, but it is certainly not the consensus that they are worth the giving. Histamine (see Hay Fever for method) has been employed with apparently considerable resultant relief by Foshay and Hagebusch (1939), and Cherry and Prickman (1941), but the latter authors recognize that much more experi-

ence must be had before the true worth of the agent can be known since in some of their cases the relief ascribed to the influence of histaminase might only have been spontaneous

PHYSICAL ALLERGY

In studies since 1928, Duke has impressed the profession with his demonstrations, confirmed by others, that any of the bizarre manifestations commonly laid at the door of neurasthenia, psychasthenia, vagotonia and so on, as well as the more orthodox allergic syndromes, may not infrequently be due to heat, effort, cold, or light sensitivity

THERAPY

Persons highly sensitive to heat from without should avoid exposure to high temperatures as much as possible, of course, and will do well to move into a cool, dry climate. Since they are nearly always susceptible to attacks as the result of internal liberation of heat also, avoidance of physical activity is a part of the treatment as well. Temporary relief can nearly always be obtained by the taking of a cold bath. Cold sensitive individuals can usually protect themselves fairly well by the use of adequate clothing and by taking care never to expose themselves to low temperatures when they cannot rather vigorously exercise at the same time. For such persons swimming, whether in an artificial pool or natural body of water, is always particularly dangerous, many individuals have doubtless drowned through unrecognized hypersensitivity of this sort. A hot bath is probably the quickest and simplest way in which to counteract the effects of chilling in cold sensitive individuals. When the patient is severely enough afflicted that the mere exposure of a small portion of the body surface, such as placing the hands in tap-water, will bring on the symptoms, the occupational phase of the malady may assume considerable importance. Duke reports that he has been able to desensitize some individuals by accustoming them to plunge into a cold bath for a few seconds every morning, in others he has employed a rapid ice rub all over the body. In other instances he has prevented an early morning attack by warming up the patient thoroughly by a hot bath at midnight. Horton *et al* (1936), at the Mayo Clinic, state that the average cold sensitive patient can be adequately desensitized by having him immerse a hand in water at 50° F for one to two minutes twice a day for three to four weeks, in some instances they have also succeeded by starting with the water at 65° F and decreasing the temperature to 45° F for increasing periods. Some of their patients have likewise been desensitized by subcutaneous injection of 0.1 mg of histamine twice daily for two to three weeks.

Recently, histaminase (methods in Hay Fever) has been successfully used in a small number of cases by Roth and Horton (1937), Vaisberg (1939), and Baker (1940), but Peters and Horton (1941) have also reported a failure.

In light sensitivity the problem is much more difficult of solution because adequate protection from exposure is practically impossible. Many

years ago attention was called to the fact that injection of hematoporphyrin into experimental animals rendered them light sensitive and practical deduction from the observation was made in pointing out that huckwheat contains phytoporphyrin a similar substance. Since this substance may also occur in ordinary wheat and in oatmeal it would seem advisable to investigate the effect of cereal free diets on light sensitive patients even though the studies of Templeton and Lunsford (1932) cast some doubt on the significance of the porphyrins in this connection. The ingestion of quinine acriflavine and other fluorescent substances as well as the taking of sulfonal or the presence of lead poisoning or liver insufficiency have all been associated with some cases. To diminish the penetration of ultraviolet rays it is stated (Jour Amer Med Assoc, 102: 1103, 1934) that 5 per cent of disodium naphthol sulfonate in solution in alcohol or in an ointment base may be effective.

DRUG ALLERGY

In recent years evidence has been accumulating that sensitization to ordinary as well as to some extraordinary drugs is a much more common occurrence than had been previously suspected. I cannot gather together here merely to list them the large number of drugs already implicated but the reader will find the chief among them discussed from this standpoint at those places in the book where such consideration seems most appropriate for example arsphenamines in syphilis cinchophens and acetylsalicylic acid (aspirin) in rheumatic affections amidopyrine in agranulocytosis the sulfonamides in the chapter on the toxicities of this group etc. Quick (1934) has proposed that drugs which produce allergic reactions such as urticaria angio-neurotic edema and vasomotor disturbance may perhaps also cause a severe inflammatory reaction terminating in necrosis comparable to the Arthus phenomenon familiar to experimental workers. The acute yellow atrophy of the liver caused in susceptible individuals by cinchophen and the granulocytopenia sometimes appearing allergically upon the ingestion of amidopyrine he would explain upon this basis. The important practical point in connection with this suggestion is that any patient experiencing urticaria that is at all related to the taking of a drug should never again be given another dose of that drug if one would not court the more serious reactions.

DEFICIENCY DISEASES

DEFICIENCY DISEASES

THE NEW DILEMMA

We are currently in an era of brilliant achievement in the nutritional field and, as always in such circumstances the literature has become very voluminous, complex, and confusing. But already the leaders in the clinical phases of this work, such men as Spies, Sydenstricker, and McLester, among others, are clearly stressing two facts: (a) the classical deficiency disease entities all have their subclassical phase which it is of utmost importance to recognize, (b) deficiency in a single nutritional factor is rare, i.e., most of the syndromes as seen by the practitioner are multiple and not single deficiencies. Add to these the third fact, namely, that in the current state of our knowledge the diagnosis of a subclassical deficiency must be made in practically all instances without the aid of either methods or instruments of precision, and we face a dilemma indeed. But I am innocent of having concocted this dilemma or equally of possessing ready at hand an easy solution for it, I merely state its existence. And one thing more I state: the evasion of responsibility through the administration of proprietary mixtures of vitamins to any patient who looks a little perked is shameful. In the pages which follow I have sought to place as much as I could consistently with the purposes of this book, of the information which would aid the practitioner in meeting the complexities of this new situation, it is my sincere hope that he will really study this material.

RICKETS

(Including Osteomalacia and Renal Rickets)

Rickets is a disease of infants which is characterized by a diminution in the inorganic phosphorus of the blood—or in those cases in which there is an associated tetany, low calcium but approximately normal phosphorus—and a faulty calcification of the newly laid down bone tissue. It is encountered most frequently between the ages of six and eighteen months, its victims being for the most part well nourished and rapidly growing children. The seasonal fluctuation of the disease is one of its most characteristic features, the case incidence rising from October to a peak in March and then falling to June, new cases very rarely develop in the summer. Rickets is most prevalent in the industrial cities of the north temperate zone and is infrequent in the tropics, indeed in subtropical regions its occurrence is unusual except in the poverty stricken class, in whom dietary deficiencies and bad hygienic habits permit the disease to exist despite the presence of plenty of winter sunshine. A typical case of rickets shows the following symptoms: restlessness, especially turning of the head from side to side, irritability, sweating of the head, enlargement of the costochondral junc-

tions, giving the rachitic "rosary," and enlargement of the epiphyses at the wrist, an abnormally open fontanel coupled with a tendency for areas of softening to develop below the occipitoparietal suture. Squareness of the head, protuberant deformity of the chest, knock knees or bowlegs and curvature of the spine, any or all of these may be present. There is often "pot belly" and usually some muscular weakness, the blood is deficient in inorganic phosphorus, and a radiograph of the lower end of the ulna shows certain abnormalities which are diagnostic.

Artificially fed infants are more prone to develop rickets than are the breast fed, though the latter are by no means infrequently attacked, prematurely born infants almost invariably become rachitic. It is felt by many pediatricians that the number of demonstrable cases of rickets, i.e., those showing some of the symptoms listed above is not an accurate index of the prevalence of the disease for it would seem possible, by careful examination to elicit one or more signs of its presence in practically all rapidly growing infants, indeed, Eliot has even suggested that this state of affairs might be physiologic. It is felt at present that rickets is caused by deficiency in vitamin D (with associated calcium phosphorus imbalance), in some other factor not yet determined, and by insufficient exposure to sunlight during the dark months. The prognosis in rickets *per se* is very good, even very pronounced deformities often disappear when the period of most rapid growth is passed and sunny "open" weather comes round again. Tetany is the most frequent and pneumonia the most serious immediate complication. The most serious residual defect is deformed pelvis in the female.

Osteomalacia which occurs almost exclusively in women in the child bearing age is generally conceded to be rickets in adults who are brought to the verge of calcium starvation by pregnancy, lactation perhaps menstruation, and possibly also in some cases (Meulengracht 1939) through disease of the digestive tract or the abuse of cathartics. The disease is not encountered in the United States but is prevalent in northern India, northern China and Japan, it occurs sporadically on the Continent, and an occasional case is seen in the British Isles. The therapy of osteomalacia requires no separate consideration from that of rickets. In the most usual of several variants of the rare childhood entity known as "renal rickets" there are roentgenographic and perhaps gross (genu valgum) evidences of rachitic changes in the bony structures but the outstanding features of the malady are dwarfism, persistent renal insufficiency due to chronic nephritis, double hydronephrosis or congenital cystic kidney, sexual infantilism if puberty is reached, hyperphosphatemia, and death from azotemia.

Some historians think that at one place in the second Iliad of Homer (circa 900 B.C.) there is a clear description of rickets. In a number of the medieval holy pictures the Christ child is shown as strikingly rachitic. But the classic description of the disease was that of Francis Glisson, in 1650, indeed, so far as I know, this was the first account to appear in medical literature. In 1908, Finlay produced the disease experimentally for the first time by the use of a deficient diet.

THERAPY

Cod Liver Oil—Clinicians have used the oil empirically for a long time with excellent results in both the cure and prevention of rickets—unless

we wish to apply the most delicate clinical tests to these results in doing which it will be found to be very doubtful if any of the antirachitic agents is able absolutely to prevent the disease. In addition to readily digestible and assimilable fats the oil contains vitamin D, which exerts a favorable influence on calcium and phosphorus metabolism and particularly in the prevention of rickets and vitamin A. The antirachitic properties of the oil reside solely in the vitamin D and are not raised by ultraviolet irradiation. The administration of the oil to mothers very much lessens the incidence of rickets in breast fed infants.

With adoption of the new U.S.P. A.I. units which are practically identical with International Units the confusing necessity of attempting a correlation of the vitamin potency of different cod liver oil preparations has disappeared. The U.S.P. standard of potency per gram is not less than 850 of the new vitamin A units and not less than 85 of the new vitamin D units and the recommended U.S.P. dose of such an oil for infants is 2 teaspoonfuls (8 cc.) daily. As a matter of fact most Council accepted (1941) oils exceed in content the vitamin D standard—the important item in rickets—and therefore in selected cases their dosage can probably be somewhat lowered with safety. The usual procedure nowadays is to begin the administration with $\frac{1}{2}$ teaspoonful of the oil when growth begins to accelerate—within two weeks of birth or at least before the end of the first month—and to increase dosage rapidly so that within a week 1 teaspoonful is being taken and in two weeks more the full dose of 2 teaspoonfuls is reached. This full dose is to be continued at least up to two years of age. Average dosage is usually somewhat augmented in the case of premature infants and in unusually rapid growing infants. In Negro and Italian infants with their marked predisposition to rickets double doses should be reached if well tolerated. Otherwise the oil should be fortified with viosterol. The only disadvantage of cod liver oil is its objectionable taste and odor. It is considered advisable to continue administering it through the summer even though there is adequate exposure to the sun because once stopped it may be impossible to get it accepted again.

Whipple (1930) finds that rancid oil is a poor source of vitamin A that it is disagreeable in taste (*more disagreeable than is!*) and that it may account for some of the digestive disturbances in infants. Her precautions in the prevention of rancidity: (a) Obtain a product in good condition. (b) Keep in refrigerator after opening. (c) Keep mouth of bottle free from dried residue. (d) Obtain only a six weeks supply at one time.

The flavoring of cod liver oil as is attempted in some of the Council accepted brands does not disturb its activity. Any of the Council accepted preparations put up with malt extract may also be used satisfactorily.

Cod Liver Oil Concentrate—There are several of these preparations which are Council accepted (1941) as equivalent to cod liver. They are marketed as oils or in capsules or tablets. Dosage varies with the amount of concentration and is therefore that which is stated on the package.

Substitute Fish Oils—The advantage claimed for burbot halibut and percomorph liver oils is that while fishy in taste they do not have the rancid taste and odor of cod liver oil. The dosage here stated is that of N.N.R. (1941) *Burbot Liver Oil* 40 drops daily or as prescribed *Halibut Liver Oil* for infants 6 to 10 drops premature and rapidly growing infants 15 drops

severe deficiencies, 20 drops or more *Percomorph Liver Oil* normal infants, 10 drops daily, curative and in severe conditions to 20 drops daily. There is also available a *Shark Liver Oil*, the dose of which is one capsule, or about 8 minims, daily. The oils are available in soft capsules.

Vioosterol in Oil—Irradiated ergosterol is the most potent of the antirachitic agents in vitamin D content (USP XI requires 10,000 units of vitamin D per gram), but it does not contain the growth promoting vitamin A. This preparation is tasteless, it may be dropped directly into the mouth or be floated on orange or tomato juice, incorporation with a feeding is considered bad practice as some of the oil may be lost on the sides of the bottle. Vioosterol (calciferol) in propylene glycol is soluble in water and hence can be mixed with the milk feeding without loss. Accepted dosage of vioosterol in oil is: average infant, 5 drops daily (standard dropper in package), premature and rapid growing infant, 15 drops, daily curative dose, 15 to 20 drops, severe cases and adults, more than 20 drops. Among the more recent studies of dosage, that of Shelling and Hopper (1936) at the Johns Hopkins Hospital is typical of all the others in fully confirming the N.N.R. dosage for full term and premature infants and is especially worth citing because it was carried out on a very large number of patients. In 134 cases of active rickets they found that dosage was intimately related to the severity of the rickets, the mild group receiving 10 drops daily, healed in five months, the group receiving 15 drops, in 4.8 months, the group receiving 20 drops, in 3.1 months. In the group receiving 30 to 60 drops healing time was not shorter, but these larger doses were given in late or very severe rickets in which smaller doses would have accomplished much slower healing. In their whole six years' experience evidence of vioosterol toxicity was never encountered.

The fear, earlier entertained, of inducing a state of toxic hypercalcemia by use of doses much larger than the above was probably unfounded since there are available many records of such high dosage administration without untoward effects, still, I think that Vollmer's (1940) use of a single massive dose of vioosterol in oil and ether, given intramuscularly, must continue to be looked upon as an experiment, though certainly a promising one. His injection mixture contains 600,000 units of vitamin D, 0.6 cc of peanut oil and 0.4 cc of ether.

Cod Liver Oil with Vioosterol—In this preparation we have oil fortified with vioosterol to obtain four and one half times as much vitamin D effect as can be obtained from the oil alone in usually tolerated doses. N.N.R. (1941) dosage: infants and young children, 2.5 to 3.3 cc daily, adults and in severe cases, up to 7 cc or more.

Halibut Liver Oil with Vioosterol—This preparation is said to be less disagreeable than cod liver oil with vioosterol and the same vitamin D effect may be obtained with smaller dosage. N.N.R. (1941) dosage (standard dropper in package) infants, 8 to 10 drops daily, premature and rapidly growing infants, 15 drops, older children, 15 to 20 drops, adults, 20 drops or more. Available also in soft capsules.

Antirachitic Milk—The Committee on Foods of the American Medical Association has had before it for some years the perplexing problem of the vitamin D fortification of milk for use in the prevention of rickets. A few years ago, however, Dr. Philip C. Jeans, of Iowa City, undertook a study of

the subject for the guidance of the Committee, and as his excellent review, published in 1936, is still the most authoritative available I shall here set down what I make out to be his conclusions on the various types of product dealt with merely adding in passing that Park (1940), of Johns Hopkins Hospital, feels that if there is doubt of these milks being an adequate source of supply in individual cases, they should be supplemented by one of the vitamin D preparations in oil—and he seems to consider it practically always wise to make this supplementation during the first year in the case of the irradiated milk and during the first six months for the fortified and metabolized milk.

Fresh Milk Containing Cod Liver Oil Concentrate—When such milk contains 400 new U.S.P. units to the quart, and is fed in customary amounts to full term infants it will prevent rickets.

Evaporated Milk Containing Cod Liver Oil Concentrate—Such milk containing 135 new U.S.P. units to the quart prevents rickets but it may permit a suboptimal intake of vitamin D as judged by calcium retention. If it contains 400 units it seems entirely adequate.

Irradiated Milk—The results with irradiated evaporated milk agree with those of irradiated fresh milk. Such milk will prevent rickets in most full term babies but the vitamin D content approaches closely the minimum preventive level and permits what is believed to be suboptimal retention of calcium.

Metabolized (Yeast) Milk—At the time of Jeans' review only one preventive study was available in which milk from cows fed irradiated yeast had been used but several studies have now appeared and such milk has been standardized at 430 units per quart.

Phosphorus—The administration of phosphorus has no legitimate place in either the prophylaxis or therapy of rickets.

Light Therapy—Rickets may be both prevented and cured when infants are exposed in the light of a good type of ultraviolet ray producing apparatus when properly used these rays like those of natural sunlight converting the provitamin in the skin 7-dehydrocholesterol into vitamin D which is then absorbed into the blood stream. It would be out of place to attempt a description of the use of such apparatus here. It is the general belief in the profession that in the temperate zone in the summer sunlight can be relied upon to prevent rickets provided the child is exposed outdoors but the study of Moore *et al* (1937) on nearly a thousand children showed that the percentage of rickets was nearly as high among the children of sunny San Diego Calif. as among those of cloudy Portland, Oregon, they therefore concluded that under modern living conditions abundant sunshine does not protect and that therefore the use of an antirachitic is advisable. Park (1940) feels that under special conditions summer sunshine may cure rickets but he thinks it should not be solely relied upon to do so. Winter sunshine is best regarded everywhere as practically nonantirachitic.

Treatment of Refractory Rickets—These cases are usually encountered in children beyond infancy. There is nothing to do but push on to enormous vitamin D dosage. Bakwin *et al* (1940) report the case of a boy who developed rickets at the age of six years in which it was necessary to use 1,000,000 units daily for cure and 440,000 units daily for maintenance. On the basis of Shohl and Butler's (1939) finding that a mixture of citric acid and sodium

citrate is in itself apparently antirachitic, it might be advisable to try such a mixture in refractory cases, these workers suggest a mixture in the proportions of two parts molar acid to one part molar salt, 50 cc of the combined solutions was used by them in infants, added to the formula as a diluent

SCURVY

Scurvy is a disease which is caused by deficiency of fresh vegetables and fresh fruits in the diet. In infants it is most frequent between the fifth and fifteenth months of life, being quite rare after the twentieth month. In adults it occurs invariably whenever there is deprivation for as much as six months of foods containing vitamin C, now identified as ascorbic (cevitamic) acid. The symptoms in adults are loss of vigor, a sallow complexion, pains in the legs principally, shortness of breath, sore, bleeding, spongy gums, foul breath, and ecchymotic spots on the skin especially of the legs. At the present time diagnosis is usually made before the condition has progressed very far, but when correction of the dietary deficiency is impossible the patient rapidly becomes a pitiable object, the body becomes edematous, dyspnea and pain are quite agonizing, intramuscular and other hemorrhages occur, enormous swelling of the gums and necrosis of the jaw take place, and death usually from intercurrent pneumonia finally comes as a blessed release. In infants the symptoms are pallor, arrest of growth and loss of weight, poor appetite, livid, swollen gums which bleed easily, and pain. This pain is manifested by a worried expression, a whimpering cry, and eversion of the thighs which are flexed on the abdomen. The most tender point is at the lower end of the femur. The pain in both infants and adults is caused by subperiosteal hemorrhages, in the former, in addition, there may be separation of the epiphyses and even fractures. In both infants and adults marked anaemia, usually of the hypochromic microcytic (iron-deficiency) type is usually, but not invariably, present. A number of cases of intracranial hemorrhage have been reported. Scott (1936) recorded a case of atypical scurvy in a girl of fourteen years whose only presenting symptom was a spontaneous subaponeurotic hematoma which gave her the appearance of having ordinary hydrocephalus.

Scurvy was unmistakably described by Jacques de Vitry in the forces of the Crusaders who were besieging Damietta in 1218, but earlier reference to the disease has not been discovered, unless a doubtful passage in Hippocrates be accepted. Always, at least since the Middle Ages, it has ravaged armies and beleaguered cities, and when long sea voyages began to be made it quickly struck at the crews of vessels. Hofmeyr (1941) has interestingly recounted how, in 1652, the Dutch made their first settlement at the Cape of Good Hope for the express purpose of supplying fresh fruits and vegetables to the scurvy-ridden crews of ships engaged in passage between Europe and the Far East. In passing, it may be of interest to note that the lime juice with which the British Navy rid itself of scurvy after 1795, and incidentally won for its crews the undying soubriquet of 'limeys,' was not lime juice at all but only the juice of the humble and far less exotic lemon. Nowadays

expeditions to far off places are protected by nothing more romantic than crystals of ascorbic acid. Scurvy caused severe losses in certain areas during World War I, being especially destructive among the British troops who were besieged at Kut-el Amara. Then, during the interim of partial and precarious world peace, the disease seemed to be endemic among adults in northern Russia and China and certain parts of the tropics only, in the latter region occurring principally, according to Manson Bahr (1940), among coolie gangs recruited for labor purposes and placed on a dietary of dried cereals and preserved foods. Now, with the planet being ravaged once more in World War II, the disease will surely take its toll again. Here in the United States, and elsewhere in lands not under the plunderer's heel it has for a long time existed principally as a problem in infant feeding though sporadic cases have been reported increasingly among adults upon whom the disjointed times have forced semistarvation in the midst of plenty. Meulengracht several years ago drew attention to the fact that scurvy is also not to be overlooked in the persons of unmarried individuals who live alone and prepare in their own rooms a diet that is nearly always deficient in the items of meat, fruits and vegetables, a number of recent reports, confirming the contention, have also shown the possibility of scurvy appearing during the course of special dietary regimens enforced during severe gastro intestinal disturbances or taken as a matter of choice by eccentric individuals. The fine study of Lund and Crandon (1941) also indicates the advisability of investigating the dietary history of patients coming to major surgery since marked vitamin C deficiency delays or even prevents wound healing. A few years ago, the newer methods of studying vitamin C levels—capillary strength tests and direct titration of ascorbic acid in blood, spinal fluid, and urine—were looked upon as great aids in the detection of subclinical scurvy. However since such tests, particularly that of the level of the acid in the blood, have shown large numbers of children to have very low vitamin C levels (Minot *et al.*, 1940, Holmes *et al.*, 1941, Milam and Wilkins, 1941) without evidences of clinical scurvy, some investigators are beginning to question the significance of such findings. In the patient of Crandon *et al.* (1940), who was on an experimental diet devoid of vitamin C for a long period, the plasma ascorbic acid level was zero for thirteen weeks before the first evidences of clinical scurvy were seen and the capillary resistance tests never did become positive. Henemann (1941) takes the position that the term 'subclinical scurvy' had better for the present be replaced by 'vitamin C deficiency,' which is purely a laboratory diagnosis.

THERAPY

Dietetic Treatment—Scurvy may be easily cured simply and solely by the addition to the diet of a sufficient amount of the antiscorbutic factor. Unpasteurized milk and raw meat contain this factor, but either must be taken in very large quantities in order to suffice (Stefansson, 1939, to the contrary, who claims that Eskimos remain free of scurvy on well-cooked meat), fresh vegetables, especially tomatoes, cabbage, green peppers, and potatoes, best serve the purpose. Orange or tomato or pineapple or grape-fruit juice are excellent, lime juice is less effective. These fruit juices, 1 or 2, two or three oranges or lemons daily (or the same number of bananas), or somewhat more than equivalent quantities of the canned juices, or the liberal use of fresh

vegetables not too long cooked, will very rapidly cure a case of scurvy. Ingalls (1939) says requirements are met by 50 cc of orange juice, or 150 cc of tomato juice, or 250 cc of pineapple juice daily but immensely much more than this must be used in severe cases. It is best in preparing the juices at home to use only glass or china receptacles as iron and copper rapidly destroy the vitamin, after more than two days of refrigerator storage fresh juice depreciates considerably even if covered. Stale vegetables are of little value, and fruits and vegetables preserved by artificially drying them are practically worthless. By new processes it has now become possible to can fruits and vegetables without destroying completely the antiscorbutic factor, the quick freezing process also preserves some of the vitamin, the commercial vogue for quick ripening by ethylene is apparently not harmful.

The disease is prevented by the same measures which suffice for cure. In the case of infants that are not being nursed by mothers *who are taking liberal amounts of antiscorbutic foods, since both the fetus and the suckling infant drain the mother's supply*, the vitamin factor must be artificially supplied after the first two weeks of life.

Somehow, perhaps by reason of the recent advances in our knowledge of the part that sunshine plays in the cure of rickets, the notion has spread that scurvy, too, is amenable to prevention and cure by the ultraviolet rays and that irradiation of foods increases their antiscorbutic properties. There is absolutely no warrant for this belief.

Ascorbic (Cevitamic) Acid—In 1928, Szent Györgyi isolated hexuronic acid from the suprarenal gland and concluded that it is identical with the reducing substance in active vitamin C concentrates. The first definite identification of the substance as vitamin C was made by Waugh and King in 1931, published in 1932. It is currently prepared from adrenal glands, and from citrus fruits, cabbage, peppers, and other plant sources, and is also produced synthetically. The Council accepted (1941) preparations are available in tablets and as crystals. The preventive dose for infants is 10 mg daily and the therapeutic dose 30 to 50 mg, for the adult these doses are 25 mg and 100 to 150 mg respectively. Since, however, there is no evidence that this vitamin is harmful in any reasonable quantities, it is a not infrequent practice to give ten times these curative doses in severe cases, part or all of this may be given intravenously dissolved in 10 cc of sterile distilled water or sterile physiologic saline solution, injecting slowly—the only record of a reaction I have seen is that of Anderson and Leake (1935), chill, fever and general discomfort in a patient given 100 mg of the drug. My feeling is that in time such high dosage will be abandoned as unnecessarily expensive except in obviously moribund patients.

Treatment of the Anemia—This matter is discussed in the section on Anemias.

PELLAGRA

When this disease develops severely and is untreated by the newer methods, its four outstanding features, which will serve to fix the characteristic picture in mind, are dermatitis, diarrhea, dementia and death. All of

these symptoms need to be somewhat elaborated upon of course. The dermatitis is sharply defined, is nearly always symmetrical, and is confined to those areas of the skin which are exposed to light, i. e., the face and neck, the backs of the hands and the lower parts of the forearms, the feet and the lower legs. The term "diarrhea" is used to indicate an outstanding feature of a large proportion of the severe cases though there is nothing characteristic of the accompanying abdominal pain, nor of the stool either except that it is usually foul and watery (vaginitis, urethritis, and endocervicitis are also frequently present). More or less severe stomatitis, glossitis, gingivitis, pharyngitis, gastritis, achylia gastrica, and enteritis are prominent features in most cases. The nervous symptoms which are so serious a part of the pellagra syndrome are so many and varied that in them as a whole may perhaps be applied the appellation "neurasthenic manifestations", but it is significant that Lewy, Spies and Aring (1940), studying 50 patients with the classical type of the disease, found that 75 per cent had polyneuropathy of the motor and sensory nerves, 20 per cent had extrapyramidal signs, of which one half showed mild Parkinsonism, and 12.5 per cent had tremor and pyramidal tract signs. In advanced cases true dementia simulating any of the well recognized psychoses not infrequently develops. Death I have set down as an outstanding feature of the disease, and so it was in patients who became definitely bed ridden in the days before the development of more or less specific vitamin therapy, in those who suffer only from a mild annually recurrent attack of the disease in an endemic area the mortality is quite low even without treatment.

The first published account of pellagra was that of Casal, in Spain, in 1735. Shortly thereafter it was recognized as a widespread malady in northern Italy, where it was exhaustively studied by Strombino in 1786-1789. At the present time it is quite prevalent in southern Europe, and the Balkan States, Poland, Asia Minor, Transcaucasia, India, Japan, China, Korea, Manchukuo, Egypt, the Sudan, Algeria, Tunis, the Red Sea coast and many regions throughout Central, West and South Africa, the West Indies, Central America, and the southern United States. Doubtless the disease can be found elsewhere for the looking, as has already been demonstrated in Canada, the British Isles, Belgium, Denmark and Germany. It is probably only lack of recognition of the entity which prevents the reporting of more cases from Malaya, Australia, and the mid Pacific islands. In the northern United States, sporadic cases had been seen as early as 1863 but its existence as a serious endemic malady in the South was not recognized until 1907 (though one should perhaps remark in passing that in her entertaining novel "Gone With The Wind," Margaret Mitchell states that physicians were recognizing the entity in the South prior to the Civil War). In the endemic areas throughout the world pellagra is principally a disease of the poor whose diet is faulty, but sporadic cases are seen everywhere in individuals of all economic classes. Practically all of these latter patients are deprived of the necessary antipellagic vitamins through one or a combination of several of the following factors: "finickiness" in eating, addiction to dietary faddism, chronic alcoholic addiction, a prolonged illness with poor alimentation or a relatively short illness with high fever, gastrointestinal pathology interfering with alimentation or absorption, pregnancy. In a very few instances, apparently associated with an excessively high vitamin requirement, an individ-

ual is seen who develops the disease even though eating and absorbing a balanced diet

In recent years Spies and Sydenstricker and their respective associates who have contributed so much to our knowledge of pellagra, have been stressing the fact that even in the endemic areas "subclassical" cases are seen, *i e*, individuals who have lesser degrees of this deficiency and do not manifest florid dermatitis, diarrhea, or dementia, but in whom some one or other of the symptoms of pellagra, often in a very modified form, lead the wary observer to suspect what he is dealing with. And these cases are encountered outside of the known pellagrous regions as well, Field *et al* (1930), reporting 9 cases of the subclassical type in Ann Arbor, Michigan, well remark that "pellagra is not confined to those two groups, alcoholic addicts and the Southern poor"

Pellagra occurs in persons of all ages, blacks and whites, and probably all other races, are equally stricken. In the endemic areas of the South cases make their appearance principally in the spring and persist until the middle of the summer. The disease 'kwashiorkor,' encountered by Williams (1935) in Accra on the Gold Coast, is believed by Stannus (1936) to be merely pellagra in children. Spies *et al* (1939) have shown here in the United States that in an area in which pellagra is endemic the disease is common among infants and children

THERAPY

The chemical breakup of vitamin B₃ into its constituent parts, nicotinic acid, riboflavin, pantothenic acid, pyridoxin (vitamin B₆), and numerous unidentifiable fractions, has supplied the means for finally proving that pellagra is a vitamin deficiency disease. But Rhoads (1939) has well pointed out that these recent triumphs should not cause us to forget that Goldberger discovered the cure for pellagra a good many years ago through demonstration of the following things: (a) that inadequate diets were uniformly eaten by human beings who contracted pellagra, (b) that such diets fed to experimental animals caused a similar disease in them, (c) that liberal diets were curative in both the spontaneous and experimental diseases, (d) and finally, that pellagra could be caused in human volunteers by feeding them deficient diets which caused the disease experimentally in animals. And the central fact in the above summary of Goldberger's findings is still true, *i e*, a deficient dietary is the cause and an adequate dietary the cure of pellagra. Even today, when by proper employment of the several fractions of vitamin B₃ arrest and apparent cure of the disease can often be accomplished without a change in dietary, it is nevertheless the burden of the testimony of the leaders in this field of study that a return to an adequate dietary is the thing to be chiefly desired not only for permanent cure of pellagra itself but also because the diet of pellagrins is one which practically always causes other deficiencies as well. The problem of pellagra in the endemic areas is an immensely complex one involving questions of food habits, food supply, living habits, money, and many other things which determine the scale of living, but it is a heartening thing to learn from Kooser and Blankenhorn's (1941) recent study that even in a community in which economic betterment has not taken place a long campaign in the health saving value of foods can be highly successful. They compared two adjacent neighborhoods with similar economic status in the mountain counties

of Kentucky. The one which got rid of pellagra has learned to have gardens, cows and chickens, and the one which still suffers pellagra has only insignificant gardens and the local grocery stores as sources of food. There is not much difference in consumption of the pellagra producing diet, i.e., both groups eat corn meal and fat pork in about equal amounts, but in the consumption of pellagra preventing foods there is a significant difference, in that the group which has freed itself of pellagra eats more fresh milk, lean pork, eggs, and chickens.

The Use of Food in Therapy—When treatment of a case of established pellagra, whether of the classical or subclassical type, is undertaken the essentials of the dietary to be enforced may be condensed from the studies of Spies and his associates into the following: a well rounded diet of 4500 calories, rich in meat, liver, eggs and milk, and if this cannot be completely followed then supplement with 75 to 100 Gm. of dry brewer's yeast daily. Recently, Spies (1941) has described his very satisfactory use of a peanut butter yeast mixture: 75 per cent of peanut butter and 25 per cent of a special 'C 50' strain of relatively palatable yeast supplied to him by the research department of one of the large breweries. The patients ate this mixture *ad libitum* at two of the daily meals, consuming an average of 60 to 75 Gm., in some instances as much as 160 Gm., per day. This mixture contains nicotinic acid, riboflavin and thiamine, and per unit weight as much carbohydrate as potatoes, more protein than steak, and one half as much fat as butter. Dr. Spies has kindly informed me that this 'yeasted peanut butter' mixture can be bought from the Andrus Scofield Co., Columbus, Ohio, and is already locally procurable in many places.

The Use of Vitamins in Therapy—When dietary correction cannot be made, or when there is reason to believe that some degree of subclassical pellagra exists in spite of the taking of an ordinarily adequate diet, or when the patient is very ill and it is necessary to accomplish arrest and cure of the condition as quickly as possible, under these conditions resort should be had to employment of vitamins in pure form. Since the showing by Lilljehjem and his associates, in 1937, that nicotinic acid is effective in curing experimental canine pellagra, and the dramatic improvement in many of the symptoms in the human form of the disease, first reported by Fouts *et al.* in the same year and subsequently by many observers throughout the world, this vitamin, nicotinic acid, has been accepted as the specific curative agent in pellagra. The improvement effected by use of this vitamin is undoubted and often dramatic, but such leaders in the clinical phases of this work as Spies and Sydenstricker find that all symptoms are not always caused to disappear in all cases, that indeed thiamine (vitamin B₁) therapy is necessary to clear the neuropathic part of the picture, and that sometimes riboflavin must also be used and in an occasional case even pyridoxin (vitamin B₆). In short, pellagra is a disease in which the outstanding deficiency is in nicotinic acid but the other elements of the B₂ complex, riboflavin and pyridoxin, may also be deficient, and furthermore a deficiency in B₁ (thiamine) is often associated with if not integrally a part of the pellagrous picture. The use of nicotinic acid alone will be described here because the other agents are elsewhere discussed: thiamine in Beriberi, riboflavin in Ariboflavinosis, pyridoxin in Pyridoxin Deficiency.

Nicotinic Acid (Amide)—The studies of Sydenstricker and Spies and their

associates have shown that the amount of nicotinic acid (now also known as "niacin") requisite for cure or maintenance is seldom predictable. Elvehjem (1940) places the normal requirement at about 25 mg daily, and it seems that a few patients with mild pellagra can be cured with this dose, "though slowly," says Sydenstricker (1941). Increasing the dose to 300 to 500 mg usually induces cure of the glossitis, stomatitis and diarrhea in about two days, the mild psychic disturbances disappear even more rapidly, though one to two weeks is often required for clearing of the cutaneous lesions. In very severe cases it is often necessary to give as much as 1000 mg for a few days, but in any type of case it is customary to reduce the dose to 100 to 150 mg daily after marked improvement has begun. After cure has been accomplished maintenance dosage is usually not required if the patient is able to obtain an adequate diet, otherwise the requirement varies with patients from 25 to 100 mg, occasionally even more.

Nicotinic acid is usually given in tablet form by mouth, when relatively small doses are given it may be taken two or three times daily after meals but when larger doses are necessary it is customary to give divided doses many times throughout the day—for example, 10 tablets of 50 mg each are spaced about an hour and a half apart in order to get in 500 mg during ordinary waking hours. A variable proportion of patients experience a reaction characterized by flushing, burning and itching sensations with increased temperature of the skin upon large dosage, the reaction subsiding after a little while and usually not being severe enough to be of any moment when dosage is spaced throughout the day. The pulse, blood pressure, respiration, and electrocardiogram are usually not affected during the reaction. Field and Robinson (1940), confirming the experience of Spies and others, found that nicotinic acid amide, used in the same dosage as nicotinic acid itself, does not cause these reactions, the amide is fully as effective as the acid, indeed it is probably in the converted form in which the acid is active in the body.

When necessary nicotinic acid may be given intravenously in the form of sodium nicotinate, Sydenstricker (1941) likes to make a solution in the proportions of 125 mg of sodium nicotinate in 200 cc of physiologic saline or dextrose solution, to avoid severe flushing reactions and waste from excretion he limits single doses to this amount and injects very slowly. For intramuscular injection Sydenstricker recommends a 10 per cent solution with 2 per cent of benzyl alcohol added to reduce pain at the site of injection. 1 cc of such solution would of course contain 100 mg of the drug.

Reactions other than the flushing above described have been occasionally noted in isolated instances: nausea, vomiting, epigastric distress, throbbing palpitation, dizziness, urticarial rash, all have been transient though some times distressing. I do not believe that such reactions have followed the use of the amide preparation.

NICOTINIC ACID DEFICIENCY ENCEPHALOPATHY

Jolliffe *et al* (1940) have reported an interesting series of 150 cases of an encephalopathic syndrome characterized by clouding of consciousness, cogwheel rigidities of the extremities and uncontrollable grasping and sucking

reflexes. This syndrome may occur alone or in association with manifestations of other deficiencies such as pellagra, beriberi, and scurvy. Patients with this malady treated by hydration alone or plus thiamine almost invariably die, patients treated by hydration plus substances rich in the vitamin B complex such as brewer's yeast and liver show a moderate drop in mortality, but when these patients are treated by hydration plus nicotinic acid a marked drop in their mortality results. Jolliffe believes it is permissible to look upon the pellagra syndrome as representing only a partial deficiency of nicotinic acid of sufficient duration to produce the structural changes recognizable in the clinical picture of pellagra, but that in the encephalopathy under discussion practically complete nicotinic acid deficiency develops so rapidly that there is no time for the development of the pellagrous picture. In these cases of course very large doses of nicotinic acid must be used and much of it, at least in the beginning, has to be given parenterally (see Pellagra for dosage and methods).

ARIBOFLAVINOSIS

(Riboflavin Deficiency)

In 1938, Sebrell discussed the possibility of clinical pellagra being a multiple deficiency and pointed out that riboflavin deficiency might occur in man simultaneously with, or independently of, pellagra. He therefore set about studying the matter, and in the same year he and Butler reported that 13 out of 18 patients to whom they gave a special diet low in riboflavin content developed the symptoms we now recognize as characteristic of ariboflavinosis, furthermore, these symptoms disappeared following the administration of synthetic riboflavin, reappeared following its discontinuance, and again disappeared following riboflavin therapy. Adequate confirmation of these findings soon appeared and we now recognize this newly discovered vitamin deficiency as an important and widespread malady. The disease occurs in all age groups, but Spies *et al* (1940) are convinced that among malnourished children in the South it occurs more frequently than any other deficiency syndrome. Sydenstricker *et al* (1940) say that it is possibly the most prevalent, without any age limitations, of all the apparently uncomplicated avitaminoses.

Many of the symptoms of which the victims of this disease complain are characteristic of all the vitamin deficiencies, namely, weakness and easy fatigability, anorexia, gastric discomfort, and insomnia, but the diagnostic signs of specific ariboflavinosis are the reddened macerated areas at the angles of the mouth known as "cheilosis," scaly greasy lesions in the nasolabial folds and on the alae nasi and ears, a specific glossitis in which the tongue is roughened and fissured and purplish red or magenta in color instead of scarlet as in nicotinic acid deficiency, a tendency for the appearance of a "shark-skin" type of eruption and seborrhea which may be very extensive pruritus ani and vulvae, and finally ocular symptoms characterized by conjunctivitis, lacrimation, burning of the eyes, mydriasis and disturbances of accommodation, and failure of vision especially in dim light. In one third of

the cases of Sydenstricker *et al* (1941) there were changes in the appearance of the iris and this group of investigators believe that at least one of the varieties of keratitis that known as rosacea keratitis is really the corneal vascularization of riboflavin deficiency.

Though due in the vast majority of instances to the taking of an inadequate diet ariboflavinosis is undoubtedly sometimes the result of gastric achlorhydria which prevents the extraction of riboflavin from foods or permits its destruction in a medium of low hydrogen ion content.

THERAPY

Schrell *et al* (1941) present data indicating that the daily intake of 8 mg of riboflavin is sufficient for a normal adult. In the experience of Sydenstricker *et al* (1941) 5 mg has been the average amount required for rapid cure of the deficiency syndrome in the presence of achlorhydria, diarrhea or severe hepatic disease. 10 to 15 mg may be required. The drug is available in tablet form (to be protected from the light) for oral administration and also in ampules whose contents may be injected intravenously in the rare instances in which this route may seem indicated. No side actions accompanying riboflavin administration have been reported.

PYRIDOXIN (VITAMIN B₆) DEFICIENCY

Since 1939 Spies *et al* have reported 24 cases in which there were residual symptoms of nutritional deficiency which could not be relieved with nicotinic acid, thiamine or riboflavin but which rapidly cleared up following the administration of pyridoxin (vitamin B₆). Smith and Martin (1940) have also reported 4 cases of cheilosis which is a part of the ariboflavinosis syndrome which cleared as well under pyridoxin as under riboflavin. Nothing very definite is known as yet regarding this deficiency except the above stated facts but the indications are that as time goes on we will fully recognize the portion of vitamin B₆ deficiency which is due to pyridoxin deficiency alone recalling (see Pellagra) that B₆ is now known to comprise nicotinic acid, riboflavin, pantothenic acid, a number of unidentifiable fractions and pyridoxin.

THERAPY

Spies *et al* (1940) gave 50 mg of pyridoxin hydrochloride intravenously. Smith and Martin (1940) from 20 to 100 mg. No toxic reactions have been reported to my knowledge.

BERIBERI

In recent years great strides have been made in our understanding of this disease which is now known to be due to thiamine (vitamin B₁) deficiency. It seems to me that from the practical standpoint the entity can be divided into three distinct types: classical, subclassical, and infantile beriberi.

Classical beriberi of the "mixed" type is characterized by peripheral neuritis, edema myocardial weakness, and enlargement of the heart. The attack usually begins slowly with malaise, palpitation and shortness of breath, gastro intestinal disturbances, and edema which usually begins in the pretibial region. Then begins the multiple peripheral neuritis which is associated with soreness of the muscles, with areas of paresthesia and superficial anesthesia, and with diminution or loss of the deep reflexes. The edema spreads up the legs, effusions appear in the serous cavities ataxia or a marked steppage gait becomes pronounced, or flaccid paralysis with muscular atrophy appears, the heart, especially the right side, becomes greatly enlarged, and the patient dies from myocardial failure due to hydropic degeneration, death coming usually after an illness of several months although demise with few or no prodromal symptoms is not rare. Pathologically the disease is characterized by degenerative changes in the peripheral nerves and also in the anterior and posterior ganglia of the cord. There are also occasional disintegrative changes in the brain cells, though mental symptoms to correspond are very rare.

A "wet" type of the disease is frequently differentiated from a "dry" type, i.e., in the former the edematous phenomena predominate over the apparent nervous system changes whereas in the latter the reverse is true. It is said that references to this classical type of beriberi are contained in very ancient Chinese and Japanese manuscripts. At present the disease is endemic in Japan, China, Indo China, the Straits Settlements, the Netherlands Indies, the Philippines, Newfoundland, Labrador, and Iceland and here and there in India, the West Indies, South America, and some parts of "native" Africa and Australia.

It was Takaki who first proved by his dietary readjustment in the Japanese navy, in 1883, that beriberi is caused by a food deficiency. He held that it was protein that was lacking in the diet but the observation of Fijkman, in 1896, that a polished rice diet always caused the disease and the subsequent researches of many investigators have shown that the missing substance is vitamin B₁, which has been isolated and synthesized as thiamine. This substance is concentrated in the outer layers of the cereals especially rice that are used for food by the native populations of large areas in the tropical and subtropical regions all around the globe, furthermore, it is removed by modern milling processes, and therefore peoples who subsist during certain portions of the year almost exclusively upon this polished rice suffer from the deprivation of vitamin B₁, that is to say, they develop beriberi. It is a mistaken idea, however, that rice eating alone will cause the disease, for it follows also upon a prolonged period of the monotonous eating of other completely milled cereals, such as wheat or corn or such a diet as white bread, molasses, sugar and fats. Likewise, too exclusive reliance upon canned foods invites the disease. In Europe and North America occasional outbreaks of classical beriberi occur in faultily managed institutions, but the number of cases is usually never large before proper dietary adjustment is made. However in 1903, Young and more recently Scott and Herrmann (1928), called attention to the fact that the *maladie des jambes* of the rice growers of Louisiana is beriberi. We are now aware also that the disease occurs sporadically with fairly high frequency throughout the whole United States and needs only to be looked for to be found, the victims in these instances being individuals

who, for one of the following reasons, ingest a diet deficient in thiamine: chronic alcoholics, who not only substitute liquor for much of their food but also require thiamine to metabolize the alcohol, and who are also likely to have gastrointestinal disturbances which interfere with absorption; the pregnant woman, whose metabolic requirement (and hence thiamine requirement) is increased by gestation, but who may nevertheless severely restrict her diet because of nausea and vomiting; patients with any type of gastrointestinal disturbance which limits ingestion, retention, or absorption of food; the use of severe elimination diets because of food sensitivities, febrile diseases in which increased metabolic requirement is accompanied by anorexia, possibly thyrotoxicosis in some instances, cirrhosis and other liver derangements which seem to inhibit utilization of thiamine, perhaps severe parenchymal damage to any internal organ may raise thiamine requirement; maintenance of a patient exclusively on intravenously or rectally administered dextrose solution, and probably in a few instances there are individuals whose thiamine requirement is higher than can be obtained from a normal dietary.

Subclassical beriberi is a term which I am applying to a type of thiamine deficiency which has little in common with the classical form of the disease since its manifestations are more nearly those to which the term 'neurasthenia' may properly be applied. I think that Willie (1940) probably expressed the feeling of many psychiatrists when he said that the neuropsychiatric implications of thiamine deficiency is a subject which is still in the uncrystallized stage but it seems to me that Williams (1941) and his coworkers have clearly shown through carefully controlled thiamine-deprivation studies that evidences of thiamine deficiency can be recognized far short of the classical signs and symptoms of beriberi. Their patients—who were carefully selected and cooperative throughout, manifested several or all of the following signs or symptoms: capriciousness of appetite sometimes going to the point of intolerance for food, low blood pressure and faint cardiac sounds, marked sinus arrhythmia, palpitation and a pulse rate exceeding normal limits on moderate exertion, giddiness associated with pallor on standing, anemia of a hyperechromic, macrocytic type, lowered basal metabolic rate, intolerance to cold, changes of behavior, the subjects becoming in most instances depressed, irritable, quarrelsome, fearful, and inefficient through confusion in thought, uncertainty of memory, and loss of manual dexterity, headache, backache, dysmenorrhea, soreness of muscles, gastric distress after meals, sleeplessness, tenseness, paresthesia, intolerance to noise and increased sensitivity to painful stimuli. Studies similar to those of Williams have been performed also by Jolliffe *et al.* (1939), with similar findings. And the amazing and important thing about both these investigations is that the diets employed were of about the quality that a shockingly high proportion of our populace is accustomed to employ routinely. The inescapable conclusion—a thesis already elaborated by Jolliffe several years ago—is that the incidence of subclassical beriberi must be high in our land.

* *Infantile beriberi* has long been recognized as a dreadful scourge in the Far East for the incidence is high and the death rate apparently over 90 per cent. It is a disease of breast-fed infants whose mothers are thiamine deficient. Methylglyoxal has been isolated from the milk of such women and currently

Echily (1941), in Hong Kong, is interestingly studying the possibility that this substance may act as a toxic agent accounting for the high mortality

THERAPY

Thiamine.—The use of the specifically deficient agent, thiamine hydrochloride, has of course revolutionized the treatment of beriberi, the use of the agent effects a dramatic alteration in the patient's condition and progress thereafter is steady and rapid to recovery. Present dosage tends to err on the side of wasting the drug rather than risking the giving of too little since, while it is generally presumed that 2 to 3 mg cover the daily adult needs in health, there has accumulated little evidence as yet to indicate how much increase is required to overcome a long standing deficiency. In fulminating cases it is the practice of most men of large experience to give the first few doses intramuscularly, subcutaneously or even intravenously. Weiss (1940) uses 20 to 30 mg three times daily, in some urgent cases Jolliffe and Rosenblum (1939) have used as much as 1000 mg in the first twenty four hours. After the patient is saturated with thiamine (the urine acquires a burnt rubber odor) dosage may be reduced to much smaller amount, such as 5 to 10 mg daily. As a matter of fact, I imagine increasing experience is going to show that doses larger than this are probably rarely necessary at any time, Jones and Bramwell's (1939) patient was in extremis but he was given only one daily intramuscular injection of 2 mg of thiamine and he lost the signs of heart failure in five days and was discharged cured in seventeen days, the total thiamine dosage having been only 30 mg. Mills (1941) has mentioned a few cases and promised a subsequent report of patients who developed symptoms resembling those of hyperthyroidism apparently as a result of thiamine therapy, cessation of the drug was followed by prompt disappearance of these symptoms. Laws (1941) and Schiff (1941) have each reported a case in which an anaphylactic type of reaction occurred in a patient apparently sensitized by repeated injections of thiamine. There would seem to me to be no reason to use the drug parenterally in the vast majority of cases since tablets of various sizes are available for oral use and prompt improvement is the proof of gastro intestinal absorption.

Diet.—The dietary requirements for the correction and the prevention of recurrence of beriberi are the following, according to Jolliffe and Rosenblum. When the patient is extremely ill, limit the diet to milk, eggs, ground liver, pureed legumes, thin whole wheat cereals, and fruit juices administered if necessary through a nasal catheter. Following improvement, or in less severely ill patients whole wheat bread should be added, the legumes need not be pureed, other vegetables and raw whole fruit should be added, and a wider variety of meats permitted with substantial portions of either liver or pork muscle included in one of the meals daily. All vitamin free foods such as unfortified white bread, pastries, alcohol, corn syrup, candy, corn starch and soft drinks should be eliminated from the diet, and vitamins other than B₁ added if they seem indicated.

NUTRITIONAL EDEMA

This is a beriberi like state which was distressingly prevalent in the blockaded countries during World War I and is very probably prevailing now in the countries conquered during the present war. There is edema of variable grade and complaint of weariness and easy fatigability. The total protein and albumin of the blood serum are below normal, but the heart is not enlarged and polyneuritis is not a characteristic symptom. The malady results from living on a diet containing insufficient protein and too much fluids and salt. Precisely how much nutritional edema there is in the world during times of relative peace, and how much of the alleged beriberi is truly this entity is not definitely known, but presumably the incidence is very high in those regions where chronic undernutrition obtains among the masses. Isolated cases were reported in all the more advanced countries during the economic slump which preceded World War II. Cases are also seen accompanying some malady in which sufficient intake or utilization of protein foods has been impossible. Epidemic dropsy, which occurs principally in restricted areas in India and is now known to be due to an adulterant of mustard oil used in the preparation of food, is not to be confused with this entity.

THERAPY

The chief aim is of course to restore the serum protein, which can usually be accomplished by employing the ordinary adequate diet, though oftentimes considerable coaxing and catering to whims will be required in persuading the patient to partake of a diet with normal protein content. Blood transfusions do not always quickly accomplish the restoration. Tube-feeding (see Index) will turn the trick, but it is a drastic measure. Occasionally there is temptation to limit radically the amount of salt in the diet, but Weech (1936) warns against the measure as it may only additionally disturb the appetite.

SPRUE

(*Nontropical Sprue, Celiac Disease [Gee Herter Heubner Disease], Idiopathic Steatorrhea [Gee Thaysen's Disease]*)

In the middle of the eighteenth century, sprue was observed and described by Hillary in the West Indies. Subsequent modern reports, by Manson in China and Van der Burg in Java, both in 1880, started us off with the fixed belief that this is exclusively a tropical disease, and obscured the two important facts that sprue had actually been described as early as 1669, by Ketelaer, occurring among Belgians in their native land, and that in the present day in temperate zones the disease need only be looked for to be found. Likewise, the curious wasting disease of children, first described as 'the coeliac affection' by Gee in England in 1868, has so many features in common with sprue that it may now also profitably be considered as identical with that malady—though there are qualified students of the subject who still object

to a consideration of these diseases nlt together as one, most notably Bennett and his associates in England. However, I feel that Thaysen of Copenhagen, the proposer of the designation "idopathic steatorrhea" and leading proponent of the unity of the several maladies was robbed of complete vindication of his viewpoint only by his untimely death in 1936. It is Snell's (1939) considered opinion that distinctions between these entities are largely artificial, and it seems to me that in his latest review, Manson Bahr (1941) is now inclining in the same direction.

Sprue, which tends to progress in a series of exacerbations is characterized by a sore and excoriated tongue, excessive intestinal fermentation, light-colored, very bulky fetid, and sometimes frothy stools, which contain fat in excess of that in the diet, a very low (flat) blood sugar curve, a reduction in calcium and phosphorus in the serum, and a blood picture regarding the formed elements, practically identical with that of pernicious anemia. The abdomen is usually distended and tympanitic, in some instances it is flaccid and has a doughy feel with the patient in the reclining position. There is usually very little abdominal pain but frequent complaint of feeling "sore from mouth to anus." Dilatation of the colon has been often noted, the demonstrations by Snell and Camp (1934) and Mackie *et al.* (1935) of characteristic roentgenologic changes in the small intestine which vary with the severity of the clinical picture and regress under specific therapy, have been confirmed. Except in the terminal stages diarrhea is not so frequent as it is exhausting. In long standing cases the victims become very cachectic and die from inanition or intercurrent disease. Excessive crossness and irritability, periodically accompanied by moderate fatty diarrhea and vomiting may be the thing which primarily brings the very young patient under medical observation (Hanes and McBryde, 1936) the adult victim also manifests evidences of nervous system involvement such as insomnia, depression, moroseness, irritability, etc.—even apparent subacute combined degeneration of the cord has been occasionally observed (Weir and Adams, 1934, Woltman and Heck, 1937).

The typical anemia of sprue is at first hypochromic and later assumes the hyperchromic macrocytic type characteristic of pernicious anemia—in adults, that is, that this shift in type does not usually occur in younger individuals is considered to be due to the fact that the bone marrow of children rarely reacts in a hyperchromic-macrocytic fashion though in adults this form of reaction results from diverse injuries. Rarefaction of bone (osteoporosis) and tetany are characteristics of the disease at all ages but stunting of growth, infantilism, fractures and bone deformities are seen more frequently in those patients whose malady began as "celiac disease" in infancy, bone pain is more often encountered in young patients, also—these differences are likely due to the greater lability and vulnerability of the bone forming mechanism in youth. Skin disturbances of various sorts are of frequent occurrence in sprue, and the abnormal pigmentation sometimes seen may closely resemble that of pellagra perhaps even suggest Addison's disease. The Van den Bergh (indirect) reaction is not increased in sprue as it is in pernicious anemia, and achlorhydria occurs no more often perhaps than in otherwise normal individuals.

It is currently the accepted opinion that the symptoms of sprue result from a functional disturbance of the small intestine which interferes with

absorption, Bennett and Hardwick (1940) refer to the state of the gut as "chronic jejuno ileal insufficiency." No satisfactory explanation for the appearance of this functional disability has been offered, but Vedder's (1940) tentative explanation of the symptoms may be summarized as follows interference with fat absorption causes the steatorrhea and later the diarrhea, later the absorption of glucose is impaired and its resulting fermentation gives rise to the distention and frothiness of the stool, diarrhea diminishes absorption of calcium and iron and of vitamins, the diminished absorption of vitamins sets up a vicious circle through aggravating the intestinal symptoms and causing still further lack of absorption.

Possibly infestation with intestinal parasites and other debilitating circumstances, predispose to the malady in the tropics

THERAPY

Liver Extract—The use of liver in sprue goes back a good many years, Castellani says that it is an old native remedy in Ceylon. Manson and many of his distinguished successors had been employing liver soup for more than thirty years before recent reiteration of the many similarities of sprue and pernicious anemia freshly introduced liver therapy in its more effective forms. This new use of liver has followed the customary methods of employment in pernicious anemia (see Index for methods), but not always with entire satisfaction until Rhoads and Miller (1934) pointed out that in sprue each case apparently has its own threshold requirement for liver substance, which must be exceeded before a remission can be established. In many instances—either because this threshold is exceedingly high, or through defective absorption—large amounts of liver by mouth are ineffective and even intramuscular injection of liver extract is unavailing, liver extract by vein, however, is life saving in these cases. Under this treatment, diarrhea ceases (Miller and Rhoads, 1936, have demonstrated roentgenologically the return of normal functional activity of the small intestine), all the other symptoms disappear, and the patient rapidly takes on weight and returns to a completely normal status. Miller and Barker (1937) stress the fact that in sprue it is nearly always necessary, however, to use larger amounts of liver extract than are required in pernicious anemia. The amount of liver extract required to maintain the patient in good health must be individually determined in each case. Impending remission is in some instances indicated by beginning changes in the blood picture, but in other patients gastrointestinal disturbances precede all other signs.

Nicotinic Acid and Riboflavin—In 1940, Manson Bahr used these two agents in a few cases of sprue and found the effects upon the tongue and upon cheilosis as good as those obtained in pellagra. He was therefore led to apply this form of therapy to sprue in general, reporting in 1941, that in the 24 severe cases of tropical sprue in which the treatment was used (300 mg of nicotinic acid daily with the addition of 3 mg of riboflavin if there was an associated cheilosis) the results were highly satisfactory. This is difficult to understand for Bing and Broager (1938), treating 2 patients with nicotinic acid, markedly altered the quantity and consistency of the feces but did not affect the other symptoms, Rhoads (1939) also says that nicotinic acid is without effect in sprue. Obviously more work is needed in this field.

Diet.—Numerous dietary regimens have had their day in sprue and even now that we are treating cases "specifically" with liver extract, diet is still considered very important. A few patients, once they have recovered under liver therapy, can maintain their health by proper dieting alone, but even if liver extract must be more or less continuously employed a rigid diet must nevertheless be adhered to. The successful diet is one essentially high in protein, with stress upon the taking of large quantities of rare red meats, and low in carbohydrate and fats. At the Hospital of the Rockefeller Institute, Miller and Barker used the following type of diet except in individuals too ill in the beginning to take it; these were given nothing but ground meat and milk until they could take the more complete diet.

Breakfast

Toast, 1 thin slice with a small piece of butter
 Fresh fruit, large serving
 Eggs, 2, prepared in any manner desired
 Milk, at least 1 large glass (this may be heated and used in place of cream for coffee or may be made into cocoa)

Luncheon

Meat, large serving ($\frac{1}{2}$ pound at least)
 Vegetables, 2, or 1 vegetable and salad
 Milk puddings, gelatin, ice-cream or fresh fruit
 Crackers (2 only) with cheese
 Milk, 1 glass

Dinner

Fruit cocktail or tomato juice
 Beef broth or any cream soup (make cream soups with milk instead of cream and omit butter)
 Meat, large serving ($\frac{1}{2}$ pound at least)
 Vegetables, 2 at least
 Desserts, as for lunch
 Milk, 1 glass

Egg nogs, milk or fresh fruit may be eaten between meals

The diet should consist largely of protein

Meat Meat should always be lean and rare

Beef, lean, either roast or steak

Lamb, lean, either roast or chops

Ham, lean

Liver, tongue, heart, kidney or sweetbreads

Fish, any fresh fish

Chicken

Lobster, crab or oysters

Milk and milk products: milk, buttermilk and American and cottage cheese

Eggs prepared in any manner desired

All fatty foods should be avoided: butter, cream, lard, olive oil and all oil salad dressing, avocado pears, pie, pastry and all foods fried in fat

All starchy foods should be avoided: potatoes, beans, corn, bread, cereals, cake and candy

Very interestingly, there have recently been reported several cases in which there has developed a bleeding tendency correctable by administration of vitamin K (see Vitamin K Deficiency). Kark *et al.* (1940) are of the opinion that hypoprothrombinemia of this sort appears only after long restriction of fatty foods; the obvious thing therefore is to supplement these diets with one of the vitamin K preparations

Iron—Observers have pointed out the necessity of adding iron to the regimen when the anemia is throughout microcytic or is converted from macrocytic to microcytic by liver therapy

Calcium, Vitamin D, Parathyroid Extract—Whatever may be the cause of the calcium deficiency of the blood in specific instances—whether there is actual faulty absorption or only excessive loss through the utilization of much calcium to form soaps with the fatty acids in the intestine—the necessity to attempt to supplement the supply is oftentimes quite apparent, indeed, in the series of patients studied by Bassett *et al* (1939) prolonged liver therapy failed to cause improvement in the absorption of calcium phosphorus, nitrogen or fatty acids, moderately high levels of calcium intake did not consistently produce a positive balance in the blood but when vitamin D was used in addition calcium absorption was obtained The methods of administering calcium are in Tetany, vitamin D in Rickets—of the latter preparations viosterol is to be preferred since the fish oils will be poorly absorbed Intensive ultraviolet light therapy is valuable also Parathyroid extract should be used very warily since it increases blood calcium only by depleting the bones Vaughan (1935) especially warns against it in cases in which there is evident bony involvement It is of interest to note that Batavia powder the ancient 'Peter Sys's Cure' extensively used in Singapore in the old days and still somewhat employed in the East generally is a proprietary preparation of lime, principally ground cuttle fish bone, I believe

PERNICIOUS ANEMIA

(See among *The Anemias*)

ALPHA TOCOPHEROL (VITAMIN E) DEFICIENCY

The alleged activity of this substance in disorders of the reproductive system is still entirely too controversial to warrant analysis here Some effect has also been claimed in amyotrophic lateral sclerosis, progressive muscular dystrophy and progressive muscular atrophy (see Index), but it is significant that only negative findings are shown in the two most recent reports—Shelden *et al* (1940) and Denker and Scheinman (1941)

TETANY

The syndrome to which this name is given is characterized principally by carpopedal spasm i.e. a tonic spasm in which the hands assume the so-called "obstetrical position" with the fingers and thumb approximated

and with contracture at the wrist, the arms are often held against the chest and if the lower extremities are involved there is flexion at the knee joint with the feet in the position of equinovarus. There are also generalized convulsions which start in the eye and face muscles and involve the whole body, with consciousness returning as soon as relaxation takes place. Laryngospasm, giving rise to a peculiar crowing sound, is a characteristic symptom. edema of the dorsal surfaces of the hands and feet is sometimes seen. When the arm above the elbow is constricted in an individual with tetany, the hand assumes the accoucheur position (Trousseau). Tapping the cheek over the facial nerve causes rapid contractions throughout its distribution (Chvostek). Use of the galvanic current elicits signs of hyperexcitability of the peripheral nerves (Erb).

By far the most frequently seen of the tetanies is that so often associated with rickets in young children, a type most likely due to decreased absorption of calcium in the absence of sufficient vitamin D. The tetany of sprue is probably also a result of failure of calcium absorption. Frank tetany during pregnancy and lactation occurs but is rare, though tetanoid manifestations such as irritability, painful cramps in the legs, insomnia, transient paresthesias and edemas are of common occurrence. This type is of course easily assumed to be due to loss of calcium, first to the fetus and then in the milk, but it is possible at least that pregnancy and lactation are merely the factors that uncover a latent tendency to parathyroid deficiency. True post-operative tetany is not often seen nowadays but its occurrence is not reckoned a mark of poor surgery, since the parathyroid glands are often eccentrically located and also apparently succumb easily at times though not considerably disturbed. In conditions of persistent vomiting and when too much alkali has either been ingested or injected there occurs a tetany associated with the state of alkalosis. Another sort of alkalotic tetany is that resulting from great loss of carbon dioxide through abnormally rapid breathing, as occasionally seen in hysterical or otherwise psychically ill persons. Ellsworth and Sherman (1930) have seen an instance of hyperventilation tetany during an asthmatic attack. A type of "idiopathic" tetany in adults is recognized—a group of cases in which none of the above etiologic associations seem to apply, however, this group is probably even much smaller than is commonly believed. Leopold and Jonas (1932) think that a critical analysis would show that most of the cases can really be classified with the infantile type due to vitamin D deficiency. It is further worthy of note, perhaps, that among the small number having no discernible cause other than a spontaneous parathyroid deficiency (comparable to the thyroid deficiency in true myxedema), diarrhea is often present though without the other symptoms of a fully developed case of sprue. Unquestionably tetany appears transiently at times at the height of serious toxic attacks, such as acute poisoning or a febrile state. Furthermore, the statement, formerly frequently made, that tetany does not occur in the newborn (*i. e.*, under two months of age) has had to be revised, for since 1931 such cases have been increasingly reported, some authors seeing several cases in a year's practice, it seems likely that tetany of this variety is due in most instances to a temporary hypofunction of the parathyroid glands, but Zahorsky (1937) thinks some of them may be alkalotic (see below) due to prelacteal feeding of alkaline mixtures. In McGavran's (1932) case the condition had undoubtedly devel-

oped *in utero* for the baby was born with every one of the symptoms of tetany and responded dramatically to the therapeutic test, he feels that many cases of so-called "birth trauma" might well have been diagnosed tetany and treated as such. McCarrison has described a form of tetany in adult natives of the Himalayas in association with goiter, it is probably the dietetic, infantile type, for upon removing to a different locality spontaneous recovery occurs.

In all of the above types of tetany there is a disturbance in calcium metabolism, with decrease in blood calcium during the period of active symptoms and rise in the same as improvement takes place, in all, that is, except the gastric, bicarbonate and hyperpneic forms, in which there is a state of alkalosis but normal blood calcium. To explain this discrepancy, we assume that the important matter in tetany is not how much calcium there is in the blood stream but how much of it is ionized, a shift to the alkaline side is thought to decrease ionization. This may be a correct explanation, as it is certainly a serviceable one, but the fact is that there has not yet been devised a method for determining the amount of calcium ion in the blood and the assumption that it is equivalent to the amount of diffusible calcium can be justified only upon the score of convenience. Since calcium deficiency and the full symptomatology of tetany are not necessarily parallel phenomena, and because chronic cases tend to become less severe (latent), it has become recognized that there are undoubtedly other factors of importance in etiology—certainly the relationship between calcium phosphorus and carbohydrate metabolism is a close one. Several groups of investigators have shown that the calcium variation can only be properly interpreted in conjunction not only with the inorganic phosphorus but with the serum protein also. Tetany does not occur characteristically in chronic nephritis, though there is often a distinct reduction in serum calcium, however, McCullagh and Ryan (1939) have recently reported an interesting case of tetany in an adult in association with renal insufficiency.

The first empiric use of calcium in tetany was probably that of Walter Harris, of London, who in 1689 "accomplished cure with no other medicines than a few ounces of crabs' eyes mixed with crystals of tartar." Shelling (1932) states that among Negroes of the eastern shore of Maryland the use of shells in the treatment of this disease has been handed down in some instances as a family secret through several generations. The first rational employment of calcium as an anticonvulsant was that of the Italian, Sabatini, in 1901.

THERAPY

Calcium Salts by Mouth—There has been an unfortunate lack of understanding of the proper method of administering calcium by mouth which, if it is now corrected, should greatly improve the results obtainable, I should think. Theoretically, calcium lactate is the ideal salt because it does not change the reaction of the tissues, but it has given very poor results as ordinarily used, i. e., taken in tablet form or stirred up in milk. Therefore calcium chloride, which is very irritating to the stomach and tends to cause acidosis is most frequently used because its very acidity promotes its absorption. But often calcium chloride, if given in tablet form or in milk, also fails to raise the calcium level of the blood and check the symptoms. It seems the

trouble lies in the fact that we have all overlooked an important piece of work of Roe and Kahn, in 1927, in which they showed that a 91 per cent rise in blood calcium could be obtained in the human by the administration of 75 grains (5 Gm) of calcium lactate dissolved in water as against only a 28 per cent rise when the same dose was given hourly for eleven hours (a total of 55 Gm) dissolved in milk. Roe (1938), in recently calling attention to this earlier work, attributes the fine results obtained with calcium lactate to the fact that the salt was not given mixed with a food which would cause an increase in the alkalinity of the intestinal tract and thus lessen calcium absorption. Wilson (1938), however, reports a case in which both calcium gluconate and calcium lactate failed to cause relief when given in milk or tablet form but in which calcium lactate dissolved in water and taken orally invariably gave as quick relief as a calcium salt given intravenously, he attributes this action to the fact that the salt was dissolved in water for oral use and not that it was not given with food.

The lesson to draw from the above, it seems to me is that we have been giving calcium salts improperly by mouth and that for best effects they should be given dissolved in considerable water, and furthermore, that when so used calcium lactate is likely to give as good account of itself as calcium chloride or calcium gluconate.

Adult dosage of calcium salts is usually 90 grains (6 Gm) or more distributed throughout the day. Sometimes ammonium chloride is also given to increase the ionization of calcium, 75 grains (5 Gm) or more daily in divided doses. Dilute U.S.P. hydrochloric acid may be used in the same way, a teaspoonful (5 cc), well diluted in water or milk, four to six times daily. It has been stated that the use of half as much lactose as calcium lactate per dose promotes the absorption of the latter, but there is not apparently much confirmation of this in clinical experience, McCullagh's (1932) is the latest report I have seen.

McGavran (1932) handled his patient, born with tetany, as follows: "Calcium chloride, 7 grains (0.45 Gm) every hour, viosterol, 3 drops every two hours, phenobarbital, 1/12 gram (0.005 Gm) every four hours. Forced feedings, 1 ounce of breast milk, every hour, were administered with a medicine dropper. It took forty five minutes out of every hour to get the ounce down. In twenty four hours the calcium chloride was stopped as it produced vomiting. The phenobarbital was stopped in forty-eight hours. In ten days the baby became a simple feeding problem and has developed so far into a perfectly normal healthy twelve months old baby."

Calcium Salts by Injection—Under urgent circumstances such as severe convulsions and glottic spasm, 5 to 20 cc of a 5 per cent solution of calcium chloride, or 10 per cent calcium gluconate, may be given intravenously, for the precautions to be observed in the intravenous administration of calcium salts, see Lead Poisoning. Subsequently, 10 cc of the gluconate solution can be given intramuscularly once or twice daily. Almost as large doses are used in infants as in adults. The local precipitation of calcium salts following the intramuscular injection of calcium gluconate in the treatment of tetany of the newborn has been reported several times. Shannon (1938) has reported 2 cases in which calcium salts were not only precipitated at the sites of injection but also at remote points in the body, reabsorption eventually occurred in both instances without known permanent damage.

Vioosterol and Fish Oils—These vitamin D preparations are used routinely in all infantile cases, there are reports of their satisfactory employment for the promotion of calcium absorption in various other forms of tetany also (See Rickets for methods of using these agents)

Dihydrotachysterol (A T 10)—This agent, introduced by Holtz (1938), in Germany, is making a good name for itself nowadays. It is a chemical substance derived from a fraction of irradiated ergosterol, hence closely related to vitamin D. The study of Albright *et al* (1938) showed that, like vitamin D, it increases calcium absorption from the gut and phosphorus excretion in the urine. In America so far it has been used principally in post operative parathyroid tetany (the most recent reports I have seen are those of Margolis and Krause, 1939, Hursthal and Claiborne, 1939, and Ryan, 1940) but Franco (1940) has used it very successfully in a case of chronic idiopathic tetany of ten years' standing in which all other types of therapy were inadequate for control and Bloxson (1940) found it ideal for treatment of a case of tetany of the newborn.

Dihydrotachysterol is marketed in 0.5 per cent solution in sesame oil and is stable but unfortunately it is still quite expensive, it is given by mouth. In severe cases of postoperative tetany some men have used as much as 10 to 20 cc daily for a few days and then sharply reduced the dosage but Ryan (1940) probably expressed what by now is the consensus in saying that in most instances even of severe tetany the dose should not exceed 2 cc daily, subsequently the maintenance dosage must be worked out in each case, some individuals require from 0.5 cc upwards daily, others do well on very small dosage only once or twice weekly. In his case of tetany of the newborn Bloxson was obliged to use 15 drops 3 times daily in order to initiate improvement. If calcium is given by mouth in addition, dihydrotachysterol dosage can be much reduced.

This is a dangerous drug because it can easily cause hypercalcemia (see symptoms under Parathyroid Extract below) and should not be used in the present state of our knowledge unless frequent observations can be made of the blood calcium and phosphate levels.

Parathyroid Extract—Though probably soon to be more or less completely replaced by dihydrotachysterol (see above), this drug has until recently been the one of choice in resistant cases of postoperative tetany. It is always supplemented by large doses of calcium by mouth. In severe cases with serum calcium values as low as 5 mg per 100 cc (the normal is 10 to 11 mg), from 40 to 60 units may be given intravenously and half the dose subcutaneously or intramuscularly four to six hours later. Probably in most cases 30 to 40 units daily will maintain the serum calcium at normal after this level has been reached but the action varies markedly in different individuals and in many cases an immunity develops after a few weeks so that even much increased doses are ineffective in influencing the blood calcium or phosphorus. Shelling and Goodman (1934) believe that in such instances we are not dealing with resistance to parathyroid but rather with factors conducive to increase in the intake of phosphorus upon the basis of very satisfactory experience in 2 cases they recommend the trial of low phosphorus diets in parathyroid tetany. Boothby and Davis (1936) also favor the use of such a diet plus calcium salts in large doses with adequate amounts of vitamin D, and only the occasional administration of parathyroid extract.

In infantile tetany the response to parathyroid has been extremely variable and perhaps upon the whole unsatisfactory. In maternal cases small doses of the extract plus calcium salts have been used satisfactorily. In 2 of Snell's (1932) 4 cases of sprue tetany the drug was effective but it failed in the other 2 indeed as he indicates the fault here is not in parathyroid insufficiency and therefore if the extract is to be used it must be fortified with full doses of calcium.

Parathyroid extract is a powerful agent and it is extremely important to guard against overdosage. Perhaps the earliest symptom is vomiting so that when this occurs in an individual taking the drug an immediate check upon the blood calcium should be made. Later there is increasing listlessness perhaps high fever and finally coma. Other than immediate cessation of the injections the treatment rests upon a very insecure foundation. Lowenburg and Ginsburg (1932) employed venoclysis to aid excretion of calcium and possibly also of parathyroid extract and to dilute the blood which at least in animals becomes very viscid and markedly decreased in volume. The administration of calcium at the same time in order to prevent decalcification seems rational.

The Treatment of Alkalotic Cases—In these cases of course the principal indication is to overcome alkalosis which is usually easily accomplished if overdosage of alkalis has been at fault. Where loss of chlorides through vomiting obtains physiologic solution of sodium chloride must be given in large quantities by all the usual channels. Ammonium chloride may be given by mouth or intravenously in amounts of 300 to 500 cc of 0.8 per cent solution first testing the solution as recommended by Cantarow to see whether it causes hemolysis. In the hyperpneic cases there is often difficulty in controlling the causative factor namely the hysterical attacks of rapid breathing in psychically disturbed individuals. In one such patient when an attack had been precipitated by excitement Meakins (1930) proved that alkalosis was the causative factor by producing instantaneous remission when the patient was caused to inhale a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The paper bag method (see Hiccup) might be expected to appeal to such patients.

XEROPHTHALMIA

This entity due to vitamin A deficiency is characterized principally by night blindness (hemeralopia) changes in the skin and certain corneal symptoms to which latter is applied the term keratomalacia. In the lands where the disease is endemic the victims are principally children or young adults. Insidiously progressive difficulty in seeing well after nightfall is usually the first evidence of the disease in rats deprived of vitamin A in the diet the disturbance has been shown to be due to failure of regeneration of visual purple in the retina. The later gross signs and symptoms are redness of the eyes lacrimation photophobia pain in the eyes wrinkling of the conjunctiva and failure of vision associated with yellowish white areas on

existence which reliably shows that such a relationship exists. Therefore, given an infant or adult on a balanced nutritious diet, nothing is to be gained in the way of protecting him from colds or other communicable diseases by adding additional vitamin A to the diet.

THERAPY

Cure is very simply and easily achieved if the patient can be placed on a diet containing sufficient vitamin A or its precursor, carotene. The eye symptoms usually abate in a few days and are completely gone in a few weeks, but the skin symptoms often require several months to disappear. The foods richest in vitamin A are milk, cream, cheese, butter, eggs, fish roe and liver. Vegetables and fruits contain carotene and must be employed in large amounts in order to make good quantities of the vitamin available, the best of these are spinach, carrots, squash, sweet potatoes, lettuce (the outer green leaves are best), peas, peppers, tomatoes, apricots and prunes. Cod and the other fish liver oils are also excellent, but viosterol and ultraviolet irradiation are worthless, since it is not vitamin D that the patient is lacking. Vitamin A is not yet clinically obtainable in pure form, but carotene has been made available. The Council accepted (1941) products for clinical use are carotene in cotton seed oil, the same with vitamin D added, and carotene with vitamin D in cod liver oil. Exact dosage has not yet been developed for these preparations, they are at present administered in about the same dose as cod liver oil of equivalent potency (see Rickets). Youmans (1939) has seen a few cases in which there was a brief exacerbation of the symptoms when use of these highly fortified oils was begun.

VITAMIN K DEFICIENCY

(Hypoprothrombinemia)

Numerous studies in recent years, principally in Denmark and the United States, have clearly revealed the fact that there are circumstances under which the supply of prothrombin in the body is below the amount necessary to insure clotting of the blood when a break occurs anywhere in the vascular system. It has furthermore been determined that these instances of hypoprothrombinemia are principally the result of deficiency in vitamin K, a factor essential to the production in the liver of this substance, prothrombin, without which clotting of the blood does not occur. Mammals including man obtain this vitamin normally from two sources. First, it is a dietary constituent, being present in particularly large amounts in such plants as alfalfa and spinach and in appreciable amounts in such green vegetables as cabbage, cauliflower, kale, carrot tops, etc. Second, it is produced by bacterial action in the lower bowel even on a diet devoid of the vitamin. It is now also available for therapeutic use in the form of relatively crude extracts obtained from alfalfa and from putrefying fish meal and a number of other substances. Recently, also, several synthetic substances with vitamin K activity have become available, for the one of these which is apparently most active—

2 methyl-1, 4 naphthoquinone—the Council on Pharmacy and Chemistry has adopted the name ‘menadione’” Prothrombin deficiencies of clinical significance are seen under the following circumstances

Liver Disturbances—The liver is of great importance in the maintenance of a normal prothrombin level for two reasons first it is the site of the formation of prothrombin a synthesis in which vitamin K, absorbed from the gastro intestinal tract, plays a vital part, and second, vitamin K is a fat soluble substance which is poorly absorbed if the liver does not pour sufficient bile into the intestine The bleeding tendency both in obstructive jaundice and in cases of biliary fistula is now recognized to be due to hypoprothrombinemia, the absorption of vitamin K being reduced in the first instance by the reduction in the amount of bile which reaches the gut, and in the second instance by the diversion of bile from the gut These matters have been elucidated largely through the observations of Quick at Marquette, Smith and associates at Iowa, and Snell and associates at the Mayo Clinic the review of Brinkhous (1940) will lead the interested reader into the literature Further than this, it now begins to seem that hypoprothrombinemia can result from liver disease *per se*, that is, without a sufficient depression or diversion of bile to prevent adequate vitamin K absorption—for example, in some instances of liver abscess or of cirrhosis No one has studied a very large group of such cases as yet but it is assumed that the bleeding tendency here is due to the inability of the liver to form prothrombin even though ample vitamin K is being absorbed from the gut

Gastro intestinal Disturbances—The Mayo group have studied a series of patients with intestinal lesions of a diverse nature intestinal obstruction, postoperative gastric retention sprue, chronic ulcerative colitis, internal and external fistulae In some of these cases hypoprothrombinemia and its consequent bleeding tendency were found, the fault lying apparently in an insufficient amount of normal intestinal mucosa for adequate absorption of vitamin K, insufficient absorption as a result of fat poor dieting in the sprue cases, prolonged diarrhea, or long-continued aspiration of duodenal contents Others have reported similar findings

Nutritional Deficiencies Other Than Sprue—Kirk and Lozner (1939) have reported 4 patients each having a dietary deficiency disease apparently unassociated with any liver disturbance in each there was hypoprothrombinemia Scurvy was diagnosed in 3 of these cases and pellagra with sub-clinical scurvy in the other It will be interesting to see whether other observers can find such cases because it is difficult to understand how the mere taking of a diet deficient in vitamin K could reduce the plasma prothrombin since the bacteria in the lower bowel are able to form the vitamin from food residues entirely devoid of it It is difficult to know just where to place the case of Rhoads and Fitz Hugh (1941) an eighteen year-old patient with a hemorrhagic diathesis extending throughout most of his life the defect appearing to be due to an ‘idiopathic’ hypoprothrombinemia coupled with an abnormality of the fibrinogen

Hemorrhagic Disease of the Newborn—It is now thoroughly established that the prothrombin level of the blood of newborn infants often drops rather precipitously during the first days of life and is then restored spontaneously The hemorrhagic episodes occasionally seen during the first few days are now generally looked upon as due to this hypoprothrombinemia, which Waddell

and Guerry (1939) were the first, I believe, to show could be effectively both treated and prevented by the administration of vitamin K (see the further discussion of this point under *therapy* below) Quick and Grossman (1939) offer as explanation of this type of hypoprothrombinemia the hypothesis that very little storage of prothrombin or of vitamin K takes place in the fetus, that exhaustion of this small amount quickly occurs after birth, and that the build up toward the normal and safe quantity only begins with the establishment in the intestine of bacteria which synthesize the vitamin, which, in the presence of bile, is then absorbed

THERAPY

Various vitamin K preparations have been prepared from alfalfa, cereals, fish meal, etc., and all have been shown to have value in effecting a quick rise in plasma prothrombin; however, since the synthetic substance, Council accepted as menadione (2 methyl-1, 4 naphthoquinone), is more potent than any of these or than any of the other closely allied naphthoquinone synthetic substances, it seems to me advisable to confine the present article to a description of the methods of employing menadione only

Liver Disturbances—At the Mayo Clinic, according to Butt (1940), patients with jaundice are divided into three groups for routine preoperative handling (a) those in whom the prothrombin time is normal, (b) those in whom the prothrombin time is prolonged (i.e., there is some degree of hypoprothrombinemia) but in whom active bleeding has not occurred, and (c) those in whom prothrombin time is prolonged and active bleeding occurs. To those with a normal prothrombin time, vitamin K is administered for two to five days before surgical intervention is undertaken, this is simply a prophylactic precaution. In those having a prolonged prothrombin time without bleeding it is often thought advisable to administer the agent through a duodenal tube. In those who are actively bleeding, whole blood transfusion is many times necessary in addition to the administration of the vitamin. Butt makes the point very strongly that despite a rise in plasma prothrombin during the first few postoperative days, the studies must nevertheless be made daily for the first four days and every second day thereafter for eight or ten more days because of the likelihood of a postoperative fall in prothrombin and the beginning of severe bleeding. This postoperative decrease in prothrombin has been remarked by many others, but its cause is not yet known. Cullen *et al.* (1940) probably find many in agreement with them that anesthetic damage to the liver is responsible; however, Allen and Livingstone (1941) studies in dogs caused them to conclude that the state does not result from the employment of the usual anesthetics (exclusive of chloroform) but is the result of inadequate preoperative use of the vitamin. Lord (1939) also using dogs, found that trauma to the liver such as might occur during difficult operations on the biliary tract, may cause a very great decrease in plasma prothrombin.

Patients are not infrequently seen who respond very sluggishly or practically not at all to vitamin K therapy. The natural inference has been that these failures were due to an impairment of the liver's ability to form prothrombin *ex vivo* when supplied with the necessary vitamin. Quick (1940) has said that it seems important now to correlate liver function and the patient's

response to vitamin K. In fact several such studies have been performed but the findings are not entirely in agreement either with each other or with clinical experience. Wilson (1939) found a high degree of correlation between liver function, as revealed by the hippuric acid test, and the plasma prothrombin concentration. This was upon the whole also the experience of Stewart and Rourke (1939), and Pohle and Stewart (1940). Smith *et al* (1939) state rather emphatically that when the liver is severely injured there is a fall of plasma prothrombin which cannot be corrected by the administration of vitamin K. However, Lucia and Aggeler (1941) find that (a) there is no significant correlation between the results of the hippuric acid liver function test and the level of plasma prothrombin, and (b) plasma prothrombin concentration may be elevated to normal by the administration of vitamin K despite markedly impaired liver function as revealed by the hippuric acid test. Butt *et al* (1940) also state that a severely damaged liver does not preclude prothrombin formation, they have seen patients who by every known clinical and laboratory test were convicted of hepatic insufficiency and who were nevertheless able to utilize vitamin K and maintain a normal plasma prothrombin level.

Oral Administration—Butt *et al* (1940) have tried dosages of menadiolone ranging from 1 to 5 mg., combined with bile salts. In average cases 1 or 2 mg. together with 5 or 10 grains (0.3 or 0.6 Gm.) of bile salts seems to suffice to elevate the prothrombin level to normal in twelve to twenty-four or thirty-six hours. The duration of such action varies with the individual case. Some men have been giving larger doses than the Mayo group, for example, all of Allen and Julian's (1940) patients received at least 8 mg. daily.

Intramuscular Administration—Andrus and Lord (1940) have been using this route with satisfaction. The agent is dissolved in corn oil, 1 mg. per cc., and sterilized in the ampule in the autoclave. They have found that in most instances the response to a single 2 mg. injection occurs in about eight hours and the effect may be prolonged for a week.

Bile salts do not have to be given when the vitamin is injected intramuscularly.

Intravenous Administration—Tocantins and Jones (1941) prepare menadiolone for intravenous use as follows: 10 mg. quantities are sterilized in dark amber ampules and kept in the dark, for use, the content of an ampule is dissolved in 1 cc. of absolute ethyl alcohol and slowly poured into 50 cc. of warm sterile physiologic salt solution in a flask wrapped in black paper. The prothrombin rise often begins within three hours of the intravenous administration of an amount of this solution containing 1 mg. of the active agent. Norcross and McFarland (1940) prepared their solutions by dissolving 10 mg. of the agent in 100 cc. of sterile hot physiologic salt solution and using as soon as sufficiently cool for injection or after storage, protected from light, in a refrigerator for only a short while. These workers find 2 mg. the minimal effective dose.

Bile salts do not have to be given when the vitamin is administered intravenously.

Gastro-intestinal Disturbances—There are no peculiarities of hypoprothrombinemia due to gastro-intestinal disturbances which require special mention from the standpoint of therapy except that of course in some of the cases absorption of the vitamin may not follow its administration by mouth.

Hemorrhagic Disease of the Newborn—In a paper published on February 28, 1942, Sanford *et al* bluntly ask the question: is administration of vitamin K to the newborn of clinical value? They studied 1693 infants over a period of two years, employing vitamin K in 711 of them—the plasma prothrombin level of the blood of these infants was raised to well above normal through the administration of the vitamin, but the frequency of hemorrhagic manifestations was just the same in the treated group as in the untreated group. This is a very startling contradiction of the findings of many men, and I think Quick did well to point out, in replying to this paper on March 21, 1942, that the injury to large vessels may be so extensive that the hemostatic defenses alone are unable to cope with the bleeding, perhaps, as suggested by Quick, the contribution of Sanford and his associates will serve principally to emphasize the fact that hemorrhage in the newborn can occur from causes other than prothrombin deficiency.

The most usual method of employing menadione to prevent the "physiologic" hypoprothrombinemia of infants (hoping thus to prevent the occurrence of the occasional case of bleeding) is that employed by Huber and Shrader (1941) in their series of 200 infants: drop 1 mg of the agent dissolved in oil on the back of the infant's tongue at six and again at thirty hours after birth, Mull *et al* (1941) like to give 1 mg at eight hour intervals for three doses. This oral type of administration will suffice for treatment also in instances in which bleeding is occurring when the infant is first seen. But there are also other methods. For example, there is the percutaneous application of the vitamin in an ointment base, as recently described by Russell and Page (1941): an amount of the ointment containing 10 mg of the agent is rubbed thoroughly on the skin of the back during the first and second days of life. Or the agent may be given intramuscularly in 1- to 2 mg doses, as in the adult. Hellman and associates (1940) at Johns Hopkins and a number of other groups since, have found that the most effective method of accomplishing the desired rise of prothrombin in the infant is to administer the vitamin to the mother, usual practice is to give 2 mg during labor but preferably this dose daily for the preceding week if opportunity permits.

The recent studies of Lawson (1941), and Willumsen *et al* (1941) indicate that intramuscular injections of whole maternal or paternal blood in the usually employed quantities of 10 or more cc at four- to eight hour intervals have very little effect in combating the hypoprothrombinemia of the newborn, even intravenous transfusion, a difficult procedure in the infant, is much less effective than vitamin K administration.

ENDOCRINE DISTURBANCES

ENDOCRINE DISTURBANCES

ENTITIES WHICH SHOULD BE LEFT TO THE SPECIALIST

There is a great stir in the field of endocrine investigation nowadays, with the result that much hullabaloo has been raised to favor the extensive employment of commercially available "hormone preparations" in treatment of the endocrinopathies. The result is that those of us who are brash and immodest enough to write books are being constantly appealed to with the plea to "straighten out" these matters—which usually means these commercial products—for the general practitioner. Sitting in the meetings of the endocrinologists, listening to the conversations of some of my friends who are of that persuasion, studying the literature, rolling things around in my mind, I come to the conclusion that most of the endocrinopathies are still susceptible of satisfactory handling only in consultation with, or entirely by, specialists in that clinical field. These gentlemen do sometimes accomplish quite satisfactory results, but no one is better aware than are they themselves what a prodigious expenditure of time, what an exhibition of diagnostic acumen derived from their special training, and what an amount of frank but cautious and above all expertly calculated therapeutic tinkering is required for them to arrive at such goals as they achieve. The following in addition to an increasingly large group of entities whose very names ring queerly in the ears of an ordinary medico, are best left alone by the general man, in my opinion: acromegaly, Simmonds' disease (pituitary cachexia), pituitary dwarfism and infantilism, Fröhlich's syndrome (adiposogenital dystrophy), pituitary basophilism, pituitary habitual abortion, pituitary lobular disorders, sterility (this entity often requires the cooperation of gynecologist and urologist as well), Dercum's disease (adiposis dolorosa), hermaphroditism, cryptorchidism (undescended testes), sexual underdevelopment, virilism, gigantism, Laurence Moon Biedl syndrome, hyperparathyroidism, adrenogenital syndrome.

ENDOCRINE THERAPY IN MENSTRUAL DISTURBANCES

(See *Menstrual Disturbances*)

CRETINISM

Cretinism is an affection originating during fetal life or in infancy, characterized by retarded mental and physical development, and due to the absence or more or less complete atrophy of the thyroid gland. Practically nothing is known of the cause of this abnormality. It occurs all over the world but is most prevalent in goitrous regions though curiously enough

it is relatively rare in North America, however, with regard to this last point, Stoddard's (1933) study indicated that in Wisconsin, and by inference in other Great Lakes regions and in the Pacific Northwest, the state of endemicity of cretinism is probably quite imminent. Among preserved records the first reference to cretinism is that of Paracelsus, in the sixteenth century, though of course the entity must have been very prevalent long before that period.

Most patients do not come under observation until they are six to eight months old because failure to develop normally is not often noticed before that age. In typical cases the general appearance is characteristic, regardless of the child's age. The hair is dry, coarse and usually scanty, the face is broad, with a wide flat nose, thick lips, protruding tongue and heavy jaw, the fontanels remain open, the forehead is low, the abdomen is large, and there is often an umbilical hernia, bony growth is delayed, but the hands and feet are large and the toes and fingers short and thick, dentition is delayed, temperature is subnormal, the skin is dry, and the tissues have a doughy feel but do not pit upon pressure. Constipation is the rule. Cretinous individuals are undersized physically and very much stunted mentally. Their characteristic response to questioning is a wrinkling grin, and their ultimate mental development is usually into a clownish sort of childishness in which they seem very happy, any type of idiocy, however, may be seen. The state of untreated cretinism is not incompatible with attainment of full years, but most victims of the affection succumb fairly early to one of the infectious diseases.

THERAPY

The response of cretins to the administration of desiccated thyroid substance (*nota bene* this substance is *not* an extract, therefore the term 'thyroid extract' is not permissible, see also the note regarding differences in brands in Myxedema) is well known to everyone. Osler has written "Not the magic wand of Prospero or the hive kiss of the daughter of Hippocrates ever effected such a change." And truly written, for the change is as rapid as it is remarkable. One needs but to start with a small dose, build it up as tolerance and necessity dictate, and then watch during the brief space required for the conversion of an imbecile into a rational being. Regarding dosage, Kerley writes from his wide experience "The required thyroid dosage is very readily learned, the child adjusts itself to the amount it requires. We usually begin with about $\frac{1}{4}$ grain twice a day, and then increase as necessary until we get results." In the beginning there is considerable loss of weight and sweating and the previously phlegmatic child becomes hyperactive, irritable and hard to manage, Wilkins (1940) says that these symptoms, which probably indicate only a slight and desirable degree of hyperthyroidism, may be disregarded. The toxic symptoms indicative of overdosage are diarrhea or cramps, vomiting, excessive irritability or twitchings, continued loss of weight, a very rapid pulse rate, and fever, when such symptoms occur, Wilkins omits the drug for a few days to a week and then resumes its use with a dose $\frac{1}{4}$ grain (0.03 Gm.) lower than that previously given. This author does not consider the apparent disappearance of all clinical symptoms as an adequate criterion of the adequacy of thyroid therapy, but is guided by the degree to which the 'bone age' and 'height age' of the patient keep pace with the

normal Unless there is continuous rapid development of the osseous system he likes to increase thyroid dosage if the patient can tolerate it, if the bone age exceeds the normal or passes too far beyond the height age the dose is decreased because when the bone age reaches that of thirteen or fourteen years epiphysial union begins and growth ceases It seems rarely to be necessary to exceed a dose of 3 grains (0.2 Gm.)

The prognosis for normal mental attainment is unfortunately not as good as for physical development, though of course the earlier treatment is begun the better the chances are As a result of their study of 29 cretins, Brown *et al* (1939) say 'a small proportion' of them may attain normal mental development In 1936, Kerley last reviewed a case on which he had several times previously reported a woman of thirty five who was competently treated from the age of two months but in whose mental development there were such gaps as inability to compose a letter or to attain any appreciation of mathematics, she reads and writes but when engaged at the latter she inserts words which have no meaning in the context, has worked for many years in the same low-grade employment because unable to take promotion However, in 1940, Kerley reported nine individuals, ranging in age from sixteen to forty years, whose development as regards not only height and weight but also mental endowment be considered normal

MYXEDEMA AND HYPOTHYROIDISM

Spontaneous myxedema is a chronic affection associated with gradual fibrosis and atrophy of the acini of the thyroid gland and characterized by impaired mentality, overgrowth of fat and connective tissue, and pronounced change in appearance The disease occurs all over the world, but is most frequent in goitrous regions It is usually seen in women at about the time of the menopause but approximately one eighth of the cases occur in men and a very small number in children Of the cause of the thyroid shrinkage practically nothing is known, it is said that the disease has a familial tendency

In the usual case of myxedema the first symptom is a gradually increasing mental sluggishness combined with a feeling of bodily weariness which is not appeased by any amount of resting The face assumes a coarsened, masklike expression, with often a transverse furrow across the forehead and an area of brownish pigmentation over the cheeks The skin is dry and scaly and the hair falls out The false edematous deposits, which do not pit upon pressure, occur in all the subcutaneous tissues, making it appear as though the patient has stored up much fat, the extremities are chiefly affected however The temperature is below normal, there is a secondary anemia and a reduction in pulse and basal metabolic rates, and the patient complains of constipation, unusual sensitiveness to cold, and pains in the muscles and joints The cholesterol level in the blood is elevated in practically all cases The occurrence of "myxedema heart" as a typical entity is now acknowledged

by most observers marked enlargement, slow feeble beat, increased circulation time, occasionally pericardial or pleural effusion, usually no gross evidences of failure—all resisting digitalis but clearing up promptly under thyroid therapy. In recent years evidence has been accumulating to show that myxedematous individuals are unusually prone to develop arteriosclerosis, chronic nephritis, arthritis, fibrous myocarditis and coronary sclerosis, but since the age of onset of many of these conditions coincides closely with that of myxedema, it is going to require very careful work to establish the interrelationship.

In recent years a number of observers have been calling attention to the probable frequency with which individuals are relegated to the scrapheap of "neurasthenia" when they are suffering from a mild hypothyroidism in which the full myxedematous picture never develops. Such patients may show one or more or none of the classical symptoms of real myxedema but it is astonishing how many other symptoms that are not usually associated in a diagnostic connection with thyroid dysfunction will clear up on specific treatment. For instance they may be underweight, not sensitive to cold or suffering from a marked dryness of skin, indeed they may not even feel mentally sluggish though they nearly always grow inordinately tired by the end of the day. Menstrual or abdominal disturbances of many types, habitual abortion or sterility, or rheumatic pains may bring them under observation. The diagnosis is more often made in women than in men but Schwittay (1941) points out that this may be partially due to the fact that menstrual disturbances are objective signs which ultimately cause women to seek medical help. Thurman and Thompson concluded a number of years ago that if in suspected cases of hypothyroidism without frank myxedema the depression in basal metabolic rate is less than 21 per cent below the average normal underfunction of the thyroid is usually not present. But that has not been the subsequent experience, at least here in the Great Lakes region, for example, Schwittay, describing his experience in Wisconsin says the results of the therapeutic test are often as dramatic when the basal rate is -8 or -10 as when it is -25 or -30 .

THErapy

In the summer of 1891, Murray described before the British Medical Association the first case of myxedema ever treated by the administration of the thyroid gland of the sheep. His patient, a woman of forty six regained good health and lived to be seventy four, dying in 1910 of heart disease. Since the reporting of this classic case, many thousands of patients have been thus treated and cured, and it has now become apparent that such failures to restore the patient to complete health as do occur are due to one or more of the following factors:

(a) *The use of a nonpotent specimen of the drug.* Hunt, corroborated by Means (1933) and Lerman and Salter (1934), has shown that there may be a great variation in the strength of the drug as prepared by different manufacturers a fact which certainly places the practitioner with his occasional case of this disease in a quandary. The only practicable solution of this difficulty is to determine the dosage with a particular preparation solely upon the basis of therapeutic results. Thyroxin is more expensive than the desiccated

cated gland substance and no more effective, it may be given by mouth or parenterally

(b) *The beginning of treatment too late in the disease* It is the exceptional case of far advanced myxedema that completely recovers under even the most careful treatment

(c) *Lack of cooperation upon the part of the patient* After a considerable degree of recovery has taken place very many individuals refuse to continue with the proper dosage required to complete and maintain their cure

(d) *The careless taking of overdoses by patients*, who, having once experienced the resultant thyrotoxic symptoms, are evermore reluctant to take sufficient doses to maintain them in a normal condition

It is the universal practice to administer thyroid substance in two stages (1) initial dosage designed to restore the patient to a normal level of metabolism, and (2) maintenance dosage, which is the smallest amount necessary to keep the metabolism within normal limits

Thyroid Dosage in Myxedema.—The patient is weighed and put to bed or at least required to spend much of the time in bed during the initial stage of treatment, and the pulse is counted each morning by the patient or some member of the family at rising time, in this way a check on the basal pulse rate is obtained with the elimination of such factors as the influence of food and muscular activity In the practice of some men dosage begins with 2 grains (0.12 Gm) of thyroid substance three times daily for five days Then the patient is weighed again and if only 2 or 3 pounds (0.9 or 1.4 Kg) have been lost, and the pulse rate is not above 80 and there are no signs of overaction, such as palpitation, dyspnea, excessive warmth, dizziness or nausea, administration may continue until a normal pulse rate is obtained or such toxic symptoms appear But this is drastic therapy and in the opinion of many men not wise Thompson (1930) usually begins with a dose of only 1 grain (0.06 Gm) daily and in individuals with arteriosclerosis or coronary disease he starts with only $\frac{1}{2}$ grain (0.03 Gm) Thereafter changes in dosage are made very gradually, in average cases in Thompson's experience $1\frac{1}{2}$ to 2 grains (0.1 to 0.12 Gm) have sufficed for maintenance Furthermore since thyroid substance acts very slowly there seems no point in giving divided dosage throughout the day

Thyroid Dosage in Hypothyroidism without Myxedema—The dosage here is about the same as in true myxedema Seward (1935) reports that about half of his patients have been able to omit the drug for a few weeks now and then without myxedematous symptoms immediately returning Hartsock (1936) makes the practical point that thyroid substance taken not later than midafternoon is not likely to induce difficulty in getting to sleep and palpitation as the patient lies down

Auxiliary Therapy—The eruptions or other reactions which sometimes accompany thyroid therapy in the beginning can at times be avoided by the simultaneous administration of small doses of the solution of potassium arsenite (Fowler's solution) Where there is an extreme degree of idiosyncrasy, desensitization must be attempted with minute doses—1/1000 grain daily to begin with and gradually increasing after a few days Where this is not practicable the thyroid substance will have to be given intermittently in as large doses as can be tolerated Paradoxically, it is sometimes necessary to use sedatives in the initial stage, particularly in the nervously unstable type

of individual; barbiturates serve well here. A number of years ago Christian warned of the special need of digitalis in cases complicated by cardiac insufficiency, for as the myxedematous condition improves more work is demanded of the heart, anemia too should be corrected. In view of the great advances made in the field of the vitamin deficiencies in recent times, it seems to me that the diet of all these people should be thoroughly investigated.

SIMPLE GOITER

Simple goiter is a diffuse, symmetrical, noninflammatory enlargement of the thyroid gland which is caused by the distention of its alveoli by an excessive deposit of colloid. Since the earliest times the view has probably been held that the incidence of this affection is in some way associated with the water supply. The Chinese of fifteen centuries B.C., as well as the Greeks and Romans of the western Classical Age, have left attestations of this belief and relatively recently "discovered" races, such as the natives of interior Africa and the American Indians, were also convinced of the relationship. However, it remained for the French chemist, Boussingault, to first propose, in 1833, the hypothesis that it is an insufficiency of iodine in food and water that is the causative factor. Boussingault actually suggested the use of iodized salt in prevention, but his observations were apparently lost sight of for when, in 1840, iodine prophylaxis was attempted in Switzerland, France and Italy, it seems to have been initiated by Chatin under the inspiration of Grange's 'new' discovery of the iodine-goiter relationship. The present theory of the association of iodine starvation and colloid goiter is due to the painstaking researches of Marine and his associates and really constitutes a 'new' discovery, for the work done during the middle of the last century had long since been forgotten. That goiter is most prevalent in regions where the water, soil or indigenous vegetables, cereals, fruits and milk are poorest in iodine is now generally recognized. In Europe these regions correspond to the Carpathian, Alpine and Pyrenean mountain ranges, in England to the valley of the Thames and Derbyshire, in South America to the Andes plateau and an area in southeastern Brazil, and in North America to the region about the Great Lakes and the St. Lawrence river, and the Cascade mountain region of Oregon, Washington and British Columbia, with less important foci in the Rocky Mountain states and those of the upper Mississippi valley. In Asia the principal endemic areas seem to be in the vast Himalayan mountain ranges and the island of Formosa though there are recent reports (Robertson, 1940) that Japanese occupation of parts of China is robbing the hinterland of its coastal supply of iodine with the result that goiter is greatly increasing in the interior. That residence near the sea is in itself a safeguard against the development of the disease, as would seem to be indicated by the relative infrequency of its occurrence along the Atlantic seaboard of the United States, is disproved by the fact of its great prevalence on the northern Pacific coast and also in New Zealand, in which latter country most of the

habitations are coastal and none more than 100 miles inland. In accepting this relationship of iodine starvation in goiter it is necessary, however, to go a step further and postulate that the disease develops only in those to whom some other as yet unknown factor or factors are operating, for it would otherwise be impossible to account for the escape of many individuals in goitrous regions and the appearance of sporadic cases in nongoitrous regions. Present animal experimentation with goitrogenic diets will probably throw further light upon the subject.

Simple goiter develops most frequently at the age of puberty and more often in girls than boys, it also not uncommonly appears in women during pregnancy and lactation. The symptoms it causes are usually few or none, save the psychic disturbances consequent upon the disfigurement. A small proportion of goiters disappear spontaneously but most of them persist to some extent throughout life. When serious symptoms arise they are usually due to the displacement of the larynx and trachea, with disturbance of respiration, or to circulatory disturbances due to pressure upon contiguous nerves.

PROPHYLAXIS

Methods—At the present time the prophylactic measures employed are the following:

1 The administration of a tablet containing $\frac{1}{2}$ grain (0.01 Gm.) of an organic iodine compound once a week throughout the school year (or throughout the duration of pregnancy). Such preparations contained in the 1941 N. N. R. are iodocasein with chocolate, chocolate tablets iodostarine, oridine tablets, stearodine tablets.

2 The addition during a period of two or three weeks twice a year of sufficient sodium iodide to the municipal water supply to bring the iodine content up to fifty parts per billion during that time.

3 The use of iodized table salt. An advisory committee of the American Medical Association has recommended that in all endemic regions a salt containing 0.01 per cent of iodine be employed (a recent analysis of 13 brands by the Wisconsin State Board of Health showed an average content of 0.014 per cent, of the 63 samples examined in Michigan, in 1939, none were found to contain less than 0.01 per cent—most manufacturers, however, advertise the content to be higher than this). It is recommended that this salt be used in cooking and at table by all persons throughout the year.

Efficacy of the Methods—Iodine was first used on a large scale in the prevention of human goiter by Marine and Kimball in the school population of Akron, Ohio, in 1917. Of 2190 school girls who took iodine for three years only 5 developed goiter, while of 2305 also observed for three years but who did not take iodine, 495 developed goiter. Since the publication of these studies numerous communities throughout the world have employed the prophylactic use of the element with a very high degree of success. It is the belief of those who have watched these studies most closely that under ideal conditions of cooperation the incidence of goiter in childhood and pregnancy could be reduced to practically nothing. Goiters developing *in utero* are also prevented. The studies of Hudson (1931) have shown that iodides given to the mother pass through the placenta and are absorbed by the thyroid of the fetus so that if a goitrous child is born of a mother who has received iodides

throughout her pregnancy it is not because of a deficiency of iodine in the fetal thyroid

Comparison of the Methods—All three of the methods are effective but Kimhall (1939) says that experience has shown the use of iodized table salt to be the most satisfactory and least expensive

Danger—The danger of inducing iodine thyrotoxicosis in adults who participate in any of the prophylactic measures is now conceded by practically all observers to be so small that it cannot be taken into practical account

THERAPY

The treatment of simple goiter by the same methods as are employed in prophylaxis sometimes accomplishes an astonishing diminution or even total disappearance of the enlargement. However, the cases of long standing goiter that are favorably affected are very few. Up to sixteen or seventeen years of age the response is better. In Marne and Kimhall's studies in Akron, Ohio, of 1182 children with goiter at the first examination who took iodine, 773 thyroids decreased in size, while of the 1048 children with goiter at the first examination who did not take iodine only 145 decreased in size.

ADENOMA

A certain number of goiters are nodular and are therefore, but perhaps erroneously, considered adenomatous. A few of these nodules have the structure of fetal thyroid and are assumed to arise from embryonal cell nests but the great majority of them seem to be encapsulated masses of adult thyroid tissue. Many observers believe these nodules to represent areas of disorderly growth in response to some unknown stimulus and that a state of hyperthyroidism can be initiated from such a nodule without diffuse involvement of the gland. However, the studies of Rienhoff, confirmed by both Dunhill and Hertzler, have considerably influenced opinion, studies in which it was shown that the involutional changes occurring in the thyroid glands of patients with exophthalmic goiter who were undergoing remission revealed striking similarities to the histologic picture seen in nodular goiter. Cole and Womack have made the same observation in their experimental production of nodular goiter in dogs. This would make of these nodules neoplasms in no sense of the word but involutional bodies whose number and size depend upon the number of remissions and exacerbations in the gland. The fact that cases of so-called "toxic adenoma" sometimes develop may simply mean that the diagnosis of toxic adenoma is made during a particularly fulminating exacerbation in a gland that has undergone many milder exacerbations and remissions. The fact that exophthalmos is unusual in these cases need not set them apart as a separate type of thyrotoxicosis for most of the cases develop after the middle thirties at which time this symptom is also unusual in the non nodular cases.

THERAPY

Most surgeons believe that all nodular goiters should be removed because of the occasional development of malignancy on a nodular base, or because of the fact that thyrotoxicosis may appear later in life. Foster comments on this attitude as follows: "This appears a radical view in the face of the fact that discrete adenomata are not rarely palpable in the thyroids of elderly persons who had recognized an abnormal gland in their necks years before. Considering the adequate supply of hazards in modern life it seems both conservative and judicious for the family physician to make an occasional examination of a young person with an adenoma of the thyroid, and reserve decision on developments." Schlesinger *et al* (1938) say that after the age of fifty years, nodules in the goiter are so common, especially in women, "as to be almost physiologic." Still, malignancy is malignancy, and since, as Clute and Albright (1936) reiterate, good scars and no mortality are to be expected after removal of a simple adenoma, the responsibility of advising against such removal is rather great. Lahey (1939) stresses the fact that the type of goiter most likely to become intrathoracic is the discrete adenoma of the lower pole of the thyroid.

Jackson and Freeman (1936) warn against giving iodine to patients with nontoxic adenomas, believing that "iodine hyperthyroidism" is sometimes induced, the subject is controversial. Means and Lerman (1935) notably being in disagreement with Jackson's viewpoint. In cases of established toxic adenoma not associated with the preceding use of iodine, Jackson advocates the use of the drug in preparation for and after operation, though he finds that only 62 per cent of the patients are benefited or not affected, while 38 per cent are made worse.

THYROTOXICOSIS

(Exophthalmic Goiter, Graves' Disease, Basedow's Disease)

Thyrotoxicosis is the name given to a peculiar complex of symptoms of which the chief are enlargement of the thyroid gland, an increase in the basal metabolic rate and a decrease in weight and strength, a characteristic nervous syndrome, exophthalmos usually, and a tendency to gastro intestinal crises of nausea and vomiting. Shurter (1933) has shown that there is a state of hypermotility of the gastro intestinal tract, the degree of which, however, is no index of the severity of the disease. The classic description of the disease is that of Caleb Parry, in 1786, though the paper of Graves, in 1835, was the first to attract wide attention. Basedow described it again in 1840. Thyrotoxicosis occurs far more often in women than in men and principally between the ages of fifteen and thirty-five. No race is entirely exempt, even in the Negro we have been shown by several observers that the state is not rare. It is believed to be a disease of relatively infrequent occurrence throughout

the world, but doubtless many mild cases are constantly being mistaken for neurasthenia, psychoneurosis, and cardiac disorders unrelated to thyrotoxicosis. The belief that the disease is more frequent in large cities than in rural districts is not supported by authoritative statistical studies, likewise, the opinion that the incidence is highest in goitrous areas lacks substantiation.

The patients are usually restless—frequently making unnecessary purposeful movements—nervous and irritable long before any other disturbances are noted. The appetite often increases during this period and there is not infrequently a gain in weight. When the patient finally visits the physician, however, she usually presents the following signs and symptoms: loss of weight despite a normal or even increased appetite, rapid pulse rate, usually accompanied by palpitation and a low diastolic pressure or perhaps a slight systolic rise, a great emotionalism either of the depressed or exhilarated type, perhaps even with the development of a pronounced psychosis, muscular tremor, especially noticeable in the extended fingers combined with easy muscular fatigue (a few cases of generalized myopathies directly associated with the disease have been reported), complaint of insomnia, excessive sweating and discomfort in warm weather, a basal metabolic rate much above the normal and not uncommonly glycosuria and hyperglycemia and impaired dextrose tolerance, usually some degree of exophthalmos and the history of a number of attacks of nausea, vomiting and diarrhea during which all the symptoms are much aggravated. Considerable thyroid enlargement is the rule and some enlargement is detectable in practically all cases. Liver function is now known to be disturbed more often than was formerly believed, but Bartel's (1939) studies indicate that hyperthyroidism *per se* does not disturb kidney function. Blood iodine is elevated in some instances and there is a tendency toward low cholesterol and serum protein levels. Hyperplasia of the thyroid tissue is the most frequent finding at autopsy, but it does not seem that this bears a constant relationship to the clinical symptomatology, for this hyperplastic state is compatible with a normal or even myxedematous condition. An increase in lymphoid tissues all over the body and hyperplasia of the thymus gland is found in most thyrotoxicosis autopsies. There are surprisingly many variations from the typical in this disease, Wohl, Lahey, and others have many times directed attention toward cases that successfully masquerade as other entities with little to call attention to the underlying thyrotoxic disturbance, even an "apathetic" type being occasionally seen.

The etiology of this disease is still unknown. One school of observers holding that the occurrences in the thyroid gland are the primary cause of the abnormal state, the other that thyrotoxicosis is a general constitutional disease, perhaps originating in a disturbance of the autonomic nervous system or an imbalance in the endocrine system (particularly an excessive secretion of the thyrotropic hormone of the anterior pituitary body), of which the thyroid symptoms are only a manifestation. The secondary etiologic role of acute or chronic infectious processes, fear, trauma, operative procedures, nervous strain, or acute nervous shock is affirmed and denied with equal fervor and authority. Occasionally a case, apparently precipitated by such a factor, will rather promptly subside upon removal of the thyroid, but in the vast majority of instances the course is a long one with remissions and relapses over many years, prediction of the duration of a remission, or the severity of a relapse, can never be made. A type of autonomic imbalance, differing from thyro

toxicosis by absence of asthenia heightened metabolic rate and loss of weight, is usually looked upon as a separate entity

THERAPY

The Importance of Rest and Diet—There are three types of treatment available in thyrotoxicosis operative nonoperative and roentgenologic in each of which rest and a full diet are essential to success Surgeons do not like to operate unless the patient has gone through a preparatory period of rest and full diet roentgenologists do undertake the handling of cases without such a preliminary period but only because their results are slowly obtained and they insist upon the institution of a regimen of rest and full diet concomitantly with their course of treatments and as regards the medical type of treatment rest and full diet are practically the whole of the therapy

Nonoperative Treatment—This is the type of treatment most frequently employed yet it is the one about whose results we know least It consists in instituting primarily a period of complete rest and full feeding to be followed by a gradual return to as near full activities as can be accomplished the sole object and aim of the method being to promote an earlier economic and social rehabilitation than occurs in the entirely untreated case It is of course based upon the assumption that thyrotoxicosis is a constitutional disease with a marked tendency to be self limited The patient is put at complete rest to bed and the attempt is made to accomplish complete mental rest as well Both these objects are often best attained in a hospital but as a matter of fact most patients are treated in the home Success will hardly crown the attempt unless the economic and other stresses under which the patient is laboring are materially reduced Often such a reduction can be accomplished by merely denying the access of certain persons to the patient but usually the difficulty is not so easily overcome The employment of sedatives is nearly always necessary at least in the beginning these drugs are discussed in Insomnia Of course the use of such stimulants as coffee and other caffeine containing beverages should be strictly forbidden

Full feeding in these cases means simply giving the patient all she will eat Usually the appetite is quite ravenous in the beginning and is best satisfied by numerous small feedings between the three full meals The theoretical value of holding down the protein content of the diet because of its specific dynamic effect is possibly to some extent supported by Jones (1940) observation that thyrotoxic individuals tend constantly to prefer a diet low in protein The advisability of a high carbohydrate diet is obvious since fuel is being so rapidly consumed in the body Recent studies are pointing to the advisability of using supplementary vitamins also in these patients Womack (1940) recently reviewing the subject feels that the chief indications are for vitamins A and B That would mean a fish liver oil or carotene to provide vitamin A thiamine (B_1) and at least nicotinic acid and riboflavin of the B_2 complex (see Index for methods)

In fortunate instances the basal metabolic rate and the pulse rate gradually fall and the patient's subjective symptoms markedly recede Under the circumstances in which this type of treatment is employed accurate and reliable basal metabolic studies with a machine cannot usually be made but many men find that the employment of one or other of the formulae utilizing

pulse rate and pulse pressure serves them as a crude, second best substitute. The simplest of the lot, that of Gale and Gale (1931), can be conveniently memorized and used, and has been found by Comroe (1935) to give results not significantly less accurate than those obtained with the more elaborate calculations of Read and Barnett. The Gale formula, to be applied under basal conditions, is $PR + PP - 111 = BMR$, where PR is the pulse rate, PP is the pulse pressure (difference between systolic and diastolic pressures), and BMR is the basal metabolic rate which is being sought.

After a variable number of weeks, *i.e.*, when it is no longer felt that anything is being accomplished by further insistence upon absolute rest, the attempt is made to return the individual slowly to her former economic status. It is freely admitted by those who champion this type of treatment that a full rehabilitation is not always accomplished, perhaps is not accomplished even in the majority of cases. I can only repeat that we have little statistical evidence of the value of this "medical" treatment. The reasons for this are obvious: it is principally employed by general practitioners who have not the follow-up facilities of the large clinics, it is not often persisted in until the program is fully executed for the reason that many individuals feel forced to resume their full activities as soon as moderate subsidence of symptoms makes this possible, and, finally, for the reason that many patients who begin such a course of treatment weary of the time consumed and yield to the promise of quicker relief held out by the surgeon.

Now regarding the inclusion of iodine in this regime, I can only say that as the years pass and convincing evidence of its safety fails to be produced one cannot avoid becoming skeptical of the wisdom of its inclusion. I know a few men who claim that their results justify them in using the drug in "medically" treated cases—in small or large doses continuously or intermittently, but usually the latter, as judgment indicates. However, surgeons are increasingly complaining that many patients are made worse by this practice, and that they are thus deprived of the opportunity to operate at the optimal time. Perhaps many men are not using the drug with intelligence but just administering it in a routine fashion and letting it go at that. I do not know. Certainly it seems that the surgeons can hack their warnings with strongly presumptive evidence, still, I feel that the whole truth is not yet known here, but am nowadays far from certain since thyroid surgery has attained its fine peak of perfection, that it is worth trying to ferret out. In short, it would seem well in the present state of our knowledge to leave iodine for pre- and postoperative use in surgically treated cases.

Indications for Operative Treatment—Lahey (1937) states that the definite conviction of himself and his associates at the Clinic is that subtotal thyroidectomy is advisable in all patients who show no progressive and convincingly obvious improvement after three to four weeks of nonoperative treatment, he feels that if all observers will not go so far, at least few will reasonably disagree with the position that all patients in whom the disease is becoming intense should be immediately operated, such intensification being indicated by progressively rising pulse rate and progressive loss of weight in a patient at rest and on full feeding. Intercurrent infection increases the severity of symptoms, often with startling suddenness. Lahey also feels that any patient with cardiac damage, as indicated by mild failures or arrhythmias, should be immediately prepared for surgery and operated without

preliminary trial of nonoperative measures, the complications of diabetes or pregnancy, either of which seriously adds to the risk of acute crisis, call for the same treatment. Lastly, any change in a patient's psychic state should be accepted as an indication of the onset of a possibly serious thyroid state, which nothing so certainly foretells as the appearance of diarrhea and vomiting. With regard to so called "iodine fast" patients, *i. e.*, patients still quite toxic after several weeks of iodine therapy, Lahey (1939) is of the opinion that it is usually advisable to perform a reasonably immediate, graded, partial thyroidectomy, the two-stage operation being less dangerous than taking such patients off iodine and waiting.

In preparing patients for operations it is probably the usual custom to give 10 minims (0.6 cc.) of compound solution of iodine (Lugol's solution) three times daily, but this treatment must be highly individualized.

Treatment of Thyroid Crises—By the term "crisis" is meant severe exacerbation of all the symptoms of thyrotoxicosis. The metabolism, fever and pulse rate rise very high; nausea, vomiting, and often diarrhea are present and excitement and restlessness not infrequently reach maniacal proportions. The administration of large amounts of fluid, dextrose and iodine are the indications here. Lahey writes as follows regarding the treatment during crisis:

"The best management of this state of severe hyperthyroidism is preventative, that is to submit patients with hyperthyroidism to surgery early, before such a severe state can occur. The next best treatment of this condition is to recognize the earliest signs of its possible appearance and to introduce intravenously 40 to 60 drops of 5 per cent glucose and fluids per minute constantly day and night, together with the frequent intravenous administration of 50 per cent glucose, the patient having from 500 to 800 grams of glucose in the 24 hours. This is best introduced into the saphenous vein just above the ankle, as delirious patients are less annoyed by this and make fewer movements with their legs than with their arms. No attempt should be made to warm the solution. We have for a number of years put 50 drops of Lugol's solution in the 1,000 cubic centimeters of fluid to be introduced intravenously and have found it a positive, satisfactory, and safe way to get iodine into these vomiting and delirious patients."

Of course in many instances the patient is able to cooperate to some extent and even to retain some fluid swallowed, in such cases it may suffice to give the iodine by mouth, giving as much as 100 to 200 cc. of Lugol's solution in the first twenty-four hours. But in any case get large amounts of readily assimilable carbohydrate into these patients, and don't forget the vitamins!

Hyperthermia must often be combated also. Means (1939) says that usually cold packs or sponging do not suffice, the ice pack or ice bath has to be used.

Lahey does not subscribe to the opinion that to operate upon the patient who has recently recovered from a crisis is to court disaster. He believes that these patients having been relieved of their immediate danger by the checking of diarrhea and vomiting should be placed on a high carbohydrate diet for two or three weeks and operated upon, usually by the 2 stage method: right subtotal hemithyroidectomy, and at the end of six weeks, left subtotal thyroidectomy.

the incidence of persistent or recurrent thyrotoxicosis after operation was 5.1 per cent, about as low figures as one finds in the literature. Crile's advocacy of denervation of the adrenals is finding few supporters in conservative groups. Rogoff (1936) has reported a case of Addison's disease following such surgical tinkering.

X-ray Treatment—Irradiation of the thyroid by those skilled in the use of this weapon can claim the following advantages over surgery: (a) The procedure is simple and will usually be accepted by all classes of patients. (b) Mild reactions characterized by nausea, vomiting and malaise and lasting only 24 to 48 hours are rare (Rose and Wolfert's, 1941, three cases of mediastinocardiac reaction are unique in the literature so far). (c) Ambulatory patients, who cannot or will not give up their usual activities, can be treated just as well as the bedfast. (d) Patients are not subjected to the psychic trauma of the preparation for operation. (e) In the event of failure it may still be followed by surgery since the alleged production of dense adhesions apparently does not increase the operative difficulties to a degree that is of any moment at all. (f) There is no appreciable mortality chargeable against the method. However, upon the whole, combined medical and surgical treatment is undoubtedly preferred by most men, some even agreeing with Hyman (1940) when he says that whatever effect is produced by roentgen therapy is due to spontaneous remission or psychotherapy, but there is no blinking the fact that present enthusiasm for operative approach is based upon the results obtainable only in certain clinics where team work has been developed to the highest point. In the rare cases of toxic goiter in children under adolescence, the consensus is against early operation. Rose *et al.* (1935) feel that the record justifies a careful trial of roentgen therapy in these cases, Poulton and Watt (1938), in England, also stress its value in young patients.

ADDISON'S DISEASE

This disease, of which only about 300 to 400 cases are annually reported in the United States, is seen almost exclusively in adults in the middle period of life. It occurs in two distinct phases, the characteristics of which are the following. *Chronic phase* the patient is asthenic, has lost weight, is hypotensive, complains of vague digestive disturbances, and possibly manifests hypoglycemic reactions, while the heart is sometimes found to be reduced in size but most importantly he exhibits dirty grayish brown hyperpigmentation of the exposed surfaces and often, sometimes exclusively, of the genitalia, anus, axillae, nipples, lips, tongue and buccal mucosa. Pigmentation is greatest over bony prominences and scars and there is often black freckling of the shoulders and neck. *Critical phase* the patient manifests, usually suddenly, the symptoms of suprarenal insufficiency, i.e., anorexia, nausea, vomiting, diarrhea, and circulatory collapse. Harrop, Loeb and their associates have shown that these crises are associated with the loss, chiefly in the urine, of

large amounts of sodium chloride the loss of sodium being greater than of chlorine. This sodium chloride loss is accompanied by blood concentration, high rise of serum potassium and of nitrogenous waste products, and reduction of the total base and carbon dioxide combining power of the blood.

Harrop (1933) suggested sodium chloride restriction to precipitate crisis in order to facilitate diagnosis in the chronic phase, subsequent adoption of the suggestion of Wilder (1937) and his associates, namely, that potassium intake be kept high during the test, has added greatly to its usefulness, but there is now full recognition that the test is dangerous and should only be conducted in hospital where there is adequate provision for emergency therapy.

Addison's disease is due to depression or destruction of one or both of the suprarenal glands. According to Snell (1935), in 80 per cent of cases there is fibrocaceous tuberculosis of the glands (Sodeman, 1930 places the proportion at 90 per cent), and in the remaining 20 per cent of cases atrophy of the glands of unknown etiology, very rarely carcinoma, gumma, hemorrhage, infarction, mycosis fungoides or chronic inflammatory changes with fibrosis of the glands have been associated with the disease in an apparent etiologic role. Snell says that in his experience at the Mayo Clinic about 1 patient in 8 has had demonstrable tuberculosis elsewhere in the body and 1 in 4 roentgenologically demonstrable suprarenal calcification. According to Kendall's (1935) showing, individuals with this disease die as the result of the development and extension of tuberculosis elsewhere in the body if they do not succumb early to the tuberculous suprarenal involvement.

THERAPY

Sodium Chloride—Of the value of a high sodium chloride intake there can be no doubt. The average daily salt intake, which in the United States is probably 6 Gm. is often augmented by an additional 6 to 20 Gm. taken in enteric-coated tablets. During crises of course large amounts of saline are administered intravenously. Wilder (1937) and his associates at the Mayo Clinic made a valuable contribution in showing that even with the administration of as much sodium as is contained in 18 Gm. of sodium chloride and 5 Gm. of sodium citrate, crisis may develop unless the potassium in the diet is kept considerably below the normal 4 Gm. intake. They proposed, and many others have subsequently used the low potassium diet opposite. The following substances must be prescribed as supplements to this diet: calcium phosphate, an iron salt, thiamine (vitamin B₁), and the principal available ingredients of the vitamin B₂ complex, namely, nicotinic acid and riboflavin (see Index for methods of employing all these agents).

Foods to be absolutely avoided according to Loeb (1941), are soups, broths, gravies, catsup, dried fruits and vegetables, bran and molasses. Meats and vegetables should be cut into small pieces and cooked in 6 to 8 volumes of water.

Desoxycorticosterone—Patients who cannot be reasonably well controlled by the use of sodium chloride and a low potassium diet must be treated with desoxycorticosterone acetate in addition, this agent being a natural steroid of the adrenal cortex which was synthesized by Steiger and Reichstein in 1937.

TABLE 10—LOW POTASSIUM DIET (WILDER ET AL.)

Potassium 16 Gm protein 57 Gm calories 2350

Breakfast

Food	Gm	Approximate measures
Orange juice	100	$\frac{1}{2}$ glass
Cornflakes	15	1 serving
Egg	50	1
Bread	50	2 slices
Butter	20	2 squares
Cream 40 per cent fat	75	$\frac{1}{2}$ cup
Coffee if desired		

Dinner

Beef tenderloin (weight uncooked)	70	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	2 $\frac{1}{2}$ squares
Cream 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		

Supper

Cheese	40	2 cubic inches
Rice (weight dry)	25	1 average serving
Tomato	50	$\frac{1}{2}$ average serving
French dressing	15	1 tablespoonful
Apple	50	$\frac{1}{2}$ average size
Bread	50	2 slices
Butter	25	2 $\frac{1}{2}$ squares
Cream, 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		

Effect—This agent affects almost exclusively electrolyte and water metabolism. The most noticeable and immediate effect is a gain in weight associated with the retention of sodium chloride and water, indeed, failure to gain weight within forty to seventy hours indicates insufficient dosage. There is a fall in serum potassium to a very low level, kidney function is improved, the patient feels, looks and behaves much better. Complete disappearance of pigmentation has not been recorded. The action of the hormone is further incomplete in that it does not correct the disturbance in carbohydrate metabolism. Thorn *et al* (1940), and others, have found that the addition of compound E (Kendall) does correct this disturbance, but this product is not commercially available.

Administration—Maintaining the daily sodium chloride supplement constant at 5 Gm, Thorn (1941) tries in the beginning the daily intramuscular injection of 2 to 5 mg of the synthetic hormone in oil. After the patient has been maintained on these injections a month or more, pellets of the crystalline hormone may be implanted subcutaneously, implanting 1 pellet of 125 mg for each 0.5 mg of hormone required by daily injection. The pellets usually providing effective therapy for approximately twelve months. Thorn describes the technic of implantation as follows: "The infrascapular region posteriorly is a convenient site for implanting pellets. Observation of strict

asepsis is imperative. The operative field is prepared with iodine and alcohol and the site of the incision is infiltrated with procaine 1:200 solution. A transverse incision 3-7 cm. in length is made a few centimeters below the inferior spine of the scapula. With blunt dissection a number (corresponding to the number of pellets) of small pockets, 3-4 cm. in depth, are prepared in the subcutaneous fat. The opening of each pocket in the subcutaneous fat is held far enough apart by a nasal dilator to permit pellets to gravitate to the bottom of the pocket without the use of force. This is very important for if the opening is too small the pellet may be crushed by the force used to insert it. The wound is closed with subcuticular sutures of fine black silk. It is possible to insert as many as 10 to 15 pellets through a single incision." Anderson *et al.* (1940), confirmed by Turness and Rowntree (1941), find sublingual therapy satisfactory; the latter's patients were given 1 mg. (6 drops) of the hormone in propylene glycol under the tongue six or seven times daily, expectorating the preparation after fifteen minutes.

Overaction and Precautions—Excessive edema may occur and may be counteracted by reduction in dosage of hormone or sodium chloride, not both simultaneously for fear of provoking crisis. Hypertension seems extremely likely to occur and to be accompanied by signs of serious cardiac overwork; dosage adjustment again is said to handle this situation. Hypoglycemic reactions are particularly likely to occur during acute infectious or gastro-intestinal disturbances. Hot weather, according to Ferrebee (1941) is likely to raise the requirement for hormone. Excessively low serum potassium levels so often occur in connection with this therapy that Tooke *et al.* (1940) were led to investigate its significance from the clinical standpoint and found that it became possible to administer the hormone practically without danger if the diet were not kept low in potassium; indeed, in some instances it even seemed advisable to supplement a normal diet with some additional potassium in the form of potassium citrate. Wilder (1940) is careful to point out that this dietary reversal applies only to patients receiving desoxycorticosterone therapy and not to those being treated with salt alone, which latter still require the low potassium diet.

Cortin—The preparation of the adrenal cortical hormone dates from the work of Rogoff and Stewart, and independently Hartman, in 1927, with subsequent refinements in methods by Hartman and Swingle and Pfaffner. "Cortin" preparations are commercially available but the dosage is very high, the cost is absolutely prohibitive save for a very few individuals and it has not been demonstrated in the satisfaction of all workers that therapy with these preparations is reliably effective. It does not seem to me that the general practitioner is likely to use "cortin," particularly now that desoxycorticosterone is available.

Ascorbic Acid (Vitamin C).—There are observations indicating the participation either of vitamin C in cortical function or of cortical function in vitamin C metabolism. The state of our knowledge is still inexact but it would seem unlikely that any harm could be done and possibly some good might accrue, from supplementing the dietary with additional ascorbic acid (see Scurvy for methods).

DIABETES MELLITUS

The islands of Langerhans in the pancreas normally secrete a hormone, insulin, which promotes in some complex way the oxidation of dextrose and its conversion into glycogen and the deposition of this glycogen in the liver and the muscles, in addition it in some way influences the conversion of protein and fat into sugar. When the production of insulin is markedly decreased, there is an increase in blood sugar above the normal amount sugar appears in the urine, and we say that the individual has diabetes mellitus. The principal symptoms are a marked increase in the amount of water drunk and food eaten, frequency of urination and oftentimes polyuria, and a loss in weight and strength which the patient finds difficulty in reconciling with his great increase in food intake—*plus sugar in the urine*. This latter symptom, or rather laboratory finding is the most important of all, for it cannot be gainsaid that it is a sound diagnostic principle to regard every person with sugar in the urine as a diabetic until he is proved not to be, *i e.*, until it is shown that the glycosuria is not one of the following types, reviewed by Marble in 1934: (a) rare true renal glycosuria (normal blood sugar but low renal threshold for sugar), (b) physiologic lactosuria during lactation, (c) fairly frequent mild glycosuria of pregnancy which disappears after parturition, (d) that glycosuria sometimes manifest during acute infectious diseases, hyperthyroidism, hyperpituitarism, malignancy, traumatic injury to the brain, carbon monoxide poisoning, general anesthesia, the use of xanthine diuretics, strychnine or morphine, (e) "alimentary" glycosuria following carbohydrate stuffing in some individuals, or after full feeding of a patient who has been starving, (f) the rare condition characterized by constant presence in the urine of small quantities of pentose, which may perhaps normally appear also after a debauch of plums, cherries, grapes, or prunes. Attempts to classify cases of diabetes as mild, moderate or severe upon the degree of any of the symptoms, and especially with regard to the amount of sugar in the urine or in the blood at the first examination, are usually unsuccessful for two reasons: first, because the patient often presents himself either after a food debauch, and consequently with a high glycosuria, or after a period of severe abstinence designed to impress the new physician with his earnestness as a patient, and second, because it is by no means infrequent for patients with an astonishingly low carbohydrate tolerance to respond remarkably well to well planned and executed treatment. That most cases of diabetes are actually mild is a truth that is becoming increasingly apparent—which is, however, by no means the same thing as saying that the disease is not a serious one even in the mildest cases.

When there is lack of insulin in the tissues—that is to say in a case of diabetes—not only is carbohydrate oxidation disturbed but there is also interference with fat catabolism and increased excretion of nitrogen as a result of protein destruction to augment the supply of dextrose. The result of the disturbance in fat metabolism is that β -oxybutyric acid and its derivatives collect in the tissues and a state of acidosis (more correctly, ketosis) is set up which, if allowed to progress, culminates in the most dreaded symptom of all—coma. The presence of these bodies is easily detectable in the urine, but the other symptoms of mild acidosis are too vague to be described here. Indeed, of coma itself the prodromal symptoms are very elusive. Any of the

following should arouse suspicion: loss of appetite, nausea and vomiting, diffuse abdominal pain, tenderness and spasm, restlessness, excitement, unusual fatigue, dizziness, ringing in the ears, and disturbances in breathing. The "coma" itself may range from a state of great drowsiness to deep unconsciousness from which the patient cannot be aroused. There is usually Kussmaul breathing, acetone breath, the appearances of marked dehydration, leukocytosis, a low plasma CO₂-combining power but a high blood content in sugar and ketone acids, a comparatively low percentage of sugar, salt and nitrogen in the urine but a high concentration of acetone and diacetic acid, poor peripheral circulation, and often a peculiar softness of the eyeball not seen in other types of coma. When there are accompanying signs of renal failure these almost invariably disappear without sequelae if the attack of coma is survived.

Extremely interesting experimental studies in recent years are indicating that disturbance in the production of the internal secretion of the pancreas which is looked upon as underlying diabetes may be in part a mere reflection of the overactivity of other endocrine glands, especially the hypophysis, thyroid and adrenals, or that there may be "anti hormones" which must be reckoned with in future investigations of the nature of insulin's action. But these things have not as yet affected practical therapy.

The most frequent time of onset is in the early fifties, but the disease may appear at any age and is distributed about equally between the sexes, an alleged preponderance to females being not yet proved. Formerly diabetes in children, in young adults, and in pregnant women was felt to have an almost hopeless prognosis, but insulin has entirely changed the status of these patients. The disease is encountered in all races, incidence is higher in Hebrews than in Goths, and in Hebrews female patients outnumbered males 2:1. In Rudy and Keeler's (1939) study of 1000 patients of that race, the incidence is higher too in the rich than in the poor. The hereditary transmission of a "tendency" for development of diabetes, as well as the contention that obesity and probably also thyrotoxicosis predispose, may tentatively be considered proved, indeed Newburgh and Cooch (1939) reported a group of individuals whose glycosuria and hyperglycemia disappeared upon correction of their obesity alone. The frequency with which chronic gallbladder disease, tuberculosis, advanced arteriosclerosis, and particularly coronary disease are diagnosed among diabetics is certainly worth remarking. Siegal and Allee (1941) have called attention to the occurrence among middle aged, mild hypertensive diabetics of a clinical syndrome closely simulating chronic glomerulonephritis, with a nephrotic phase and often terminating in renal failure. Despite the fact that the literature is replete with reports of "acute" cases, it is still the consensus that in the majority of instances the onset is gradual. Diabetes incidence is trending upward throughout the world, in civilized lands, mortality is decreasing in childhood and early adulthood, but it is increasing in late middle and old age, especially among women.

In the Sanskrit manuscript of Susruta (fifth century, A.D.) the principal symptoms of this disease are noted and the entity is given a name which translates into "honey urine." The observations were several times confirmed by Christian and Mohammedan writers of the medieval period but it was only in 1776 that Matthew Dobson proved that the sweetness of blood and urine was actually due to the presence of sugar.

THE DIETETIC PROBLEM IN DIABETES TREATMENT

The average normal individual performing the amount of daily work described by the expression "up and about" requires a dietary containing the proportional amounts of protein, carbohydrate and fat, and supplying the total number of calories (4 deriving from each gram of protein, 9 from each gram of fat, and 4 from each gram of carbohydrate), shown in the first of the group of tables at the end of this article. The diabetic differs from such a normal individual in that, because of the shortage of insulin in the blood, the tissues cannot utilize to the full the principal source of calories in the food, *i.e.*, the carbohydrates. Therefore the chief problem in the treatment of diabetes is the rearrangement of the diet to provide only such amount of carbohydrate as can be satisfactorily oxidized by the body, the patient obtaining nevertheless enough energy producing food to support life on an endurable plane. Attempt must be made to meet the caloric requirements by increasing either the amount of protein or of fat, or of both in the diet. To what extent may this be accomplished with the proteins? Only to a very moderate extent for the following reasons: (a) the specific dynamic action of protein is so high that, in employing it in sufficient amount to overcome appreciably the shortage in carbohydrate, the total caloric need would be so much increased that the dilemma would become more rather than less trying; (b) the amount of protein that would have to be eaten would be so great that the diet would be entirely unpalatable for more than a very short period; (c) and finally, this protein in the course of catabolism would yield 58 per cent of itself in the form of carbohydrate to tissues that are already surfeited with carbohydrate which they are unable to use. As compared with protein, fat has three advantages: first, each gram yields 9 rather than 4 calories; second, its specific dynamic action is lower than that of protein, thus enabling it to be used without so greatly increasing the total caloric need; and third, only 10 per cent of it is converted into carbohydrate in the course of catabolism. But its disadvantages are unfortunately grave. Of the two disadvantages of fat the least important, but by no means unimportant one is the fact that fat, in large enough amount to raise the total calories to a point approaching satisfaction, is very repugnant to the gastrointestinal tract and often provokes a most undesirable state of indigestion. But the chief disadvantage is this: fat needs carbohydrate for its proper catabolism. Somewhat less than 1 Gm. of carbohydrate must be simultaneously utilized for each gram of fatty acid that is oxidized—"fat burns in the fire of carbohydrate," it has been said. But in the diabetic, in whom not much carbohydrate can be burned, what happens to the fat? Simply this: that such amount as cannot "burn in the fire of carbohydrate" is not fully metabolized but stops when the ketone bodies are formed. These ketone bodies are poisonous in that they attach themselves to basic radicals from which they displace the weaker carbonic acid, thus bringing about the presence of CO_2 in excess in the blood. If this goes on in only a small way, surplus CO_2 is eliminated through the lungs and some of the ketone bodies are passed out through the kidneys; but if protein is being kept as high as is thought to be necessary for the body needs, and the carbohydrate tolerance is very low, then the attempt completely to make up the caloric deficit with fat will finally and inevitably lead to acidosis and coma.

Prior to the advent of insulin for parenteral use in 1920 both horns of this dilemma were grasped firmly if ineffectually by simply starving the patient. If his carbohydrate tolerance was very low and he could not bear large amounts of protein and fat for the reasons which have just been presented he was merely placed on that amount of carbohydrate protein and fat which he could utilize—and thus was kept living though hardly alive. The condition of these undernourished patients was in severe cases deplorable in the extreme and they usually died in a short time either directly or indirectly from undernutrition or from coma following the breaking of an intolerable dietary regimen. Then came the discovery of insulin, which made possible the utilization of carbohydrate and thus also the feeding of more fat and the therapy of severe diabetes was reborn. It is essential for the reader to understand that the new order of things is in the fullest sense only a rebirth of the old Diet is today as it was in the Naunyn or Allen period the bedrock upon which all the structure stands but because of insulin the severe diabetic is now able to live a reasonably comfortable life provided he has associated with him someone—mother sister wife nurse always a woman—interested and untiring in the application of the great detail of dietetic and insulin control. (One is obliged to add parenthetically however that this may not always be the case see the description of the bold new type of therapy which I have called the relative disregard of sugar treatment under *Protamine Zinc Insulin*.)

ADVANTAGES OF THE HIGH CARBOHYDRATE-LOW FAT METHOD OF TREATMENT

Beginning with the studies of Geyelin and Sansum and their associates in 1906 the new liberal diet has subsequently gathered great momentum through many favorable reports. It is now employed successfully by large numbers of physicians in all lands and I am here describing it to the exclusion of all other types of treatment believing it to be the method best suited to the needs of the general practitioner. The following are the steps which led toward the adoption of high carbohydrate low fat therapy and the reasons for the satisfaction which attends its use.

Basis of Treatment before Insulin—Allen and his associates had shown that by removing variable proportions of the pancreas in the dog they could cause diabetes of varying severity which the animal survived if given just that amount of carbohydrate which the reduced amount of islet tissue could handle but that if he were fed liberally he succumbed because the islet tissue rapidly degenerated. This was the birth of the undernutrition and pancreatic rest type of treatment.

Introduction of Insulin—When insulin arrived on the scene its use was merely engrafted upon the above treatment i.e. the tolerance of the patient was determined by building up the carbohydrate after starvation to the amount he could utilize and then insulin was added to enable him to take a little more carbohydrate for a little more comfort.

Desertion of the Traditional Formula—During the periods just mentioned the apportioning of the carbohydrate (C) protein (P) and fat (F) fractions of the diet was dictated by the formula $F = 2C + \frac{1}{2}P$ by which Woodyatt had made clinically available the laboratory researches of Shaffer. But as time

went on and experience increased, the following clinical observations made it apparent that the principle needed considerable revision (1) Patients so strictly managed were always perilously close to ketosis and therefore at all times in a more or less potentially dangerous condition (2) Patients who did not take the thing too seriously and now and then moderately indulged in excess carbohydrate often escaped acetonuria despite the development of glycosuria (3) With a little sugar in the urine the patient usually felt better (4) The ultimate demonstration that, by utilizing to the fullest extent the pancreas resting function of insulin, carbohydrate could be raised and fat lowered out of all relation to the formula with a tremendous increase in both safety and well being of the patient

Insulin Reduction Accomplished—No very definite relation having been found between insulin and the various types of food when the use of full diets was begun, the assumption was made that an increase in carbohydrate

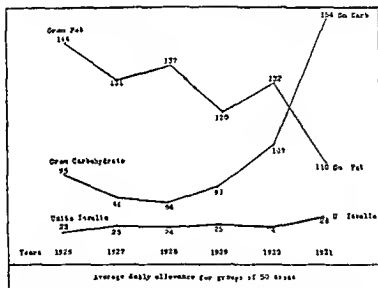


Chart showing alteration in C-P-F and insulin relations on changing to high carbohydrate-low fat diets (Joseph H. Barach, J.A.M.A., April 9, 1932)

would necessitate a proportionate increase in insulin dosage, and Sansum therefore proposed the injection of 1 unit of insulin for each 2 Gm. of food, i.e., a patient eating 400 Gm. of food was to be given 200 units of insulin. Surprisingly, this proportional insulin increase has not been found to be necessary, all who use the new methods being in agreement that the addition of a few more units beyond a certain minimal amount, which varies with individual cases, will take care of astonishingly large increases in carbohydrate. The accompanying chart of Barach, though now ten years old, nevertheless still shows this better than any more recent graphic presentation I have seen. Note that in 1928, with 84 Gm. carbohydrate and 137 Gm. fat, 24 units of insulin were required, whereas in 1931, on 154 Gm. carbohydrate (practically twice the former amount) and 110 Gm. fat (a reduction of 27 Gm.), 28 units sufficed (an increase of only 3 units). As example, in an individual case the carbohydrate was increased from 85 to 200 Gm. daily from April, 1930, to

July, 1931, and the fat reduced from 170 to 115 Gm. At the beginning of treatment the patient required 42 units of insulin daily (25-0-17), at the time of the report, early in 1932, he was taking 40 units (22-0-18). There had also been an increase of 19 Gm. protein, so that at the time of the last report he was taking 195 Gm. more carbohydrate, 10 Gm. more protein, 55 Gm. less fat, and 2 units less insulin. In him and in others I have repeatedly seen an increase in fat followed by glycosuria, at other times he is sugar normal (absence of glycosuria with normal blood sugar). Gray and Sansum's (1933) 1095 patients showed an average increase in tolerance during their seven years' use of the new diets, as also Geyelin's (1935) 150 patients treated over a ten year period. Rahinowitch reports a comparison of five years on the new diets with five years on the old diets, revealing a daily average of 10.6 units of insulin instead of the earlier 31.8 units. Peck's (1936) patients permit an average reduction of 6.4 units per day, so that he feels he is achieving twice the insulin efficiency with the new diets.

Greater Practicability—The diets are more palatable, they are cheaper and easier to prepare, they are more nearly normal, and they maintain the patient in a stronger condition—a stoker or plowman can stoke or plow—and feeling thoroughly at ease. Insulin reactions are fewer and less severe. It has also been remarked that upon the new type of therapy patients who formerly had persistently high blood sugars are seen less frequently, and that the refractory diabetic responds more 'normally'.

Reduction in Complicating Vascular Changes—There is some evidence that the new diets may be effective in reducing the incidence of arteriosclerosis and also in lowering hypertension, but it is very difficult to be certain about these things. Rahinowitch and his associates believe that the fall in blood cholesterol incident to the reduction in fat is responsible for this, Sansum *et al.* attribute it rather to the reduction of general acidity brought about by the large amounts of fruits and vegetables included in the higher carbohydrate diets.

Explanation of the Results—Theoretical substantiation of the observed clinical improvement of patients on the new diets has lagged somewhat. Adlersberg (1932) inclined toward the belief that it is due to reduction in calories, but this is not likely since the improvement persists even though many more calories are added in carbohydrates than are subtracted in fats. The suggestion of Graham *et al.* (1932), interesting, namely, that the presence of ketone bodies in the blood under the old dietary régime caused an increased demand for insulin just as the presence of staphylococcal infection, for instance, will do. Himsworth (1934) found that in the normal subject the giving of carbohydrate raises the efficiency of both pancreatic and injected insulin, and Ellis (1934) showed that at least in some diabetics this occurs also to diabetics needing large amounts of insulin. Ellis gave dextrose by mouth and small doses of insulin hourly, with the result that the amounts of insulin necessary to hold the blood sugar within normal limits decreased progressively. It would therefore seem permissible to say, at least tentatively, that the diabetic's improvement on a high carbohydrate diet is not due to stimulation of his insulin producing tissue but rather that the giving of much carbohydrate makes him more sensitive, more responsive, to his own and to the injected insulin. In fact, however, this is more restatement than explanation.

BARACH'S SIMPLE METHOD OF DIETARY COMPUTATION

(The necessary Tables are all at the end of the article)

Beginning the Diet—In the first of the tables find the patient's age and the pounds indicated as ideal for him at his height (Part I), compromising for build, weight history, and family weight tendency. Convert into kilograms (Part II). Then turn to Part III and multiply the grams of carbohydrate, protein and fat for his age and activity by this kilogram figure. The diet is begun with these daily amounts. For actually arranging meals from these figures, the second table is to be employed. The following will illustrate.

J. K., male, aged fifty, height 5 feet, 10 inches, has been diagnosed as diabetic and requires to be treated. The portions of the tables indicated by the letters contain the successive steps. (a) At fifty, and 5 feet, 10 inches, the desired weight would be 172 pounds (170 pounds for a woman). (b) This is equivalent to 78 Kg. (c) Seventy eight multiplied by the number of grams of carbohydrate, protein and fat for the adult male diabetic gives a daily allowance of 234 Gm. carbohydrate, 78 Gm. protein and 117 Gm. fat. (d) With a daily allowance of 234 Gm. carbohydrate, the patient may take 300 Gm. of 6 per cent fruit, 40 Gm. cereal (dry weight), and 60 Gm. white bread for breakfast, 170 Gm. 20 per cent vegetable, 200 Gm. 0 per cent fruit and 60 Gm. white bread for lunch, 170 Gm. 20 per cent vegetable, 200 Gm. 0 per cent fruit and 200 Gm. 6 per cent fruit, and 40 Gm. white bread for dinner in the evening. In obtaining the carbohydrate portion he will also have obtained 20 Gm. protein (the lowest figure in the 230 Gm. column). Therefore (e) When seeking the protein component, deduct this 20 Gm. from his allowance of 78 Gm. and allow him the amount of protein indicated in the 58 (i.e., 00) Gm. column, that is, he will have 100 Gm. meat for each of the three meals. Now he was to be given 117 Gm. fat, but in obtaining the protein he has incidentally obtained 60 Gm. of fat—therefore, (f) the remaining fat is to be derived as shown in the 57 (i.e., 55) Gm. column in the "Additional Fat Portion" table, this additional fat to be distributed more or less equally between the three meals.

The remaining tables comprise carbohydrate exchanges, percentage fruits and vegetables, and meat exchanges, and a final table draws attention to other useful dietary details. The patient may exchange some 6 per cent fruit or vegetable for a glass of milk by merely omitting the amount of carbohydrate and meat therein specified, or, if he does not care for 100 Gm. meat with each meal, he may exchange a portion of it for fish, or cheese, or canned salmon, and gain some butter in the trade. There is considerable opportunity for introducing variety into the menu.

Building Up the Diet—When sugar free on the initial diet for three days, with or without insulin, add 10 Gm. carbohydrate and deduct 4.5 Gm. fat from the total diet, and repeat this until hyperglycemia or glycosuria appears. In patients becoming sugar free without insulin, it may be possible to increase the carbohydrate considerably since it was begun at only about one half the normal amount, when tolerance is reached insulin may not be necessary in these mild cases. After an insulin patient has been sugar free for one month, try again substituting 10 Gm. carbohydrate for 4.5 Gm. fat without changing the insulin, and continue exchanging toward the normal diet until hyper-

"hollowness" in the stomach accompanied by great hunger, subjective and objective trembling restlessness and temporary loss of memory, sweating and pallor or flushing of the face, and increased pulse rate. These symptoms may be experienced very suddenly or they may come on gradually during the course of a quarter hour. In the more severe reactions the face assumes a masklike expression, there is diplopia and complete disorientation, and the patient may become unconscious and show a profound fall in temperature and blood pressure, epileptiform convulsions are also seen in some instances. Likewise a wide variety of behavioristic and mental changes foreign to the patient's normal personality may be manifested. Deaths have been reported but they are rare. Unquestionably a very few of the reactions are allergic in nature for they follow the use of one brand of insulin but not the use of another. Other things being equal the thin, frail, feeble patient is the most likely to develop reactions. Delayed absorption of food can certainly lead to hypoglycemic shock in a patient who has taken insulin before eating since emotional disturbance is the chief cause of such delay. The advisability of maintaining as perfect emotional balance as possible for diabetics, especially at mealtimes, has been fully established.

glycemia or glycosuria appears. Later, if tolerance improves, increase the carbohydrate or reduce the insulin.

If there is acetone and diacetic acid *without* glycosuria, too little carbohydrate is being given and both additional carbohydrate and insulin are necessary. If there is acetone and diacetic acid *with* glycosuria, fat and protein must be reduced, and carbohydrate and insulin are imperatively needed.

INSULIN

Dosage and the Timing of Injections—When the patient has been placed upon the diet computed as discussed in the preceding pages, he is studied for his ability to utilize carbohydrate. If he does not become sugar free (no sugar in urine and blood sugar not to exceed 125 mg. per 100 cc.), the use of insulin must be considered. The frequently employed practice of giving 1 unit for each 2 Gm. of dextrose output in the urine seems to find support in Miller and Allen's (1939) attempted mathematical evaluation, still it is well to bear in mind that there are many variables which can affect the relationship, and to employ this rule of 1 to 2 as only a crude approximation.

Barach finds the following a useful rough guide to insulin dosage: if the urine contains 2 per cent or more of sugar (red color in Benedict test), give 15 to 20 units three times daily. If the urine contains 2 per cent or less of sugar (yellow color in test), 10 to 15 units three times daily. If the test turns green, only a trace of sugar is present.

There need usually be no fear in using the drug boldly and freely if necessary in the beginning, for under the new high carbohydrate low fat plan of treatment it will certainly be possible to decrease very considerably the initial dosage if it has been very high. The amount of insulin reduction frequently permitted has been discussed earlier in this chapter. If only a single dose is being given, many practitioners prefer to have it taken twenty to forty minutes before breakfast, though if this is insufficient another must be taken before dinner in the evening and occasionally also before lunch, very rarely is a fourth injection necessary. Since 1930, when Sindoni studied the effects of injecting before instead of after meals, a number of men have found that in certain patients they obtain better results, better blood sugar levels, and fewer insulin reactions by having the patient inject from thirty minutes to an hour after the beginning of the meal. A practical point here is that the nervous type of individual always fearful lest something will prevent him getting his meal at the proper interval after injection, is much more at ease when all his senses and the weight of the family as witnesses combine to assure him that he is actually replete with food when the insulin begins its work.

Technic—Insulin is deeply injected subcutaneously, the site being changed so frequently that the same spot is not used more often than once a month. It is well to have patients map out all available sites in order to avoid duplications. The sites usually used are the anterior aspects of the legs, the deltoid and triceps regions of the arms, the upper portions of the buttocks, and the abdominal wall. When, as may occasionally happen, it is necessary to add 0.1 cc. of 2 per cent procaine hydrochloride solution to the insulin, epinephrine should not be used as is the usual custom with procaine.

Systemic (Hypoglycemic) Reaction—When an overdose of insulin has been taken the patient experiences a feeling of general muscular weakness,

'hollowness' in the stomach accompanied by great hunger subjective and objective trembling restlessness and temporary loss of memory sweating and pallor or flushing of the face and increased pulse rate These symptoms may be experienced very suddenly or they may come on gradually during the course of a quarter hour In the more severe reactions the face assumes a masklike expression there is diplopia and complete disorientation and the patient may become unconscious and show a profound fall in temperature and blood pressure epileptiform convulsions are also seen in some instances likewise a wide variety of behavioristic and mental changes foreign to the patient's normal personality may be manifested Deaths have been reported but they are rare Unquestionably a very few of the reactions are allergic in nature for they follow the use of one brand of insulin but not the use of another Other things being equal the thin frail feeble patient is the most likely to develop reactions Delayed absorption of food can certainly lead to hypoglycemic shock in a patient who has taken insulin before eating since emotional disturbance is the chief cause of such delay the advisability of maintaining as perfect emotional balance as possible for diabetics especially at mealtimes has been fully established

The insulin reaction is commonly ascribed to a sudden hypoglycemia but it is well not to overlook the fact that some other mechanism may also be involved since not all individuals in whom the blood sugar falls very considerably experience such a reaction indeed John has described such reactions with a normal or increased percentage of blood sugar Tishy believes that not so much the hypoglycemia *per se* as the relatively greater dextrose impoverishment within the cell is to be held accountable Müller and Petersen look upon an acute disturbance of the autonomic nervous system as the cause of the shock of which hypoglycemia is only one of many symptoms It is not unlikely also that some disturbance of the circulation in the brain takes place for a number of cases of hemiplegia have been reported as having occurred during very severe reactions

Dextrose—Any carbohydrate out of which glucose (dextrose) may be quickly formed in the body is the antidote Orange juice is usually taken by the patient at home and it acts very well One or 2 lumps of sugar depending upon the size of the individual quickly dissolved in the mouth is also effective in overcoming the symptoms If the patient is unable to swallow easily, honey or corn syrup may be used In any case after a rest the dose should be repeated

Intravenous injection of dextrose may be made if the patient is unconscious, also it must sometimes be resorted to in patients who have not lost consciousness but in whom the hypoglycemia seems to be accompanied by a depression in the absorptive power of the intestinal mucous membrane (or should the failure to respond to the oral administration of dextrose be ascribed to acute peristaltic lapse?) Not more than 25 Gm should be given in this way in a solution of 5 to 50 per cent strength—500 cc of 5 per cent 250 cc of 10 per cent 125 cc of 20 per cent 50 cc of 50 per cent usually smaller amounts suffice but occasionally larger quantities need to be given Joslin *et al* (1940) say that in severe cases in which consciousness did not return within an hour it would probably be advisable to employ constant intravenous administration of 10 per cent dextrose solution to keep the blood sugar level at approximately 200 mg per cent

The intracardiac injection of dextrose has been reported in one case by Immerman "The pulse was fast falling and the patient was moribund. Because of difficulty experienced previously in entering the veins of this patient, it was not deemed wise to attempt to do so now, as any further delay might be fatal. An intracardiac injection was decided on as the very last resort. This was accordingly done by means of the sterile syringe and the lumbar puncture needle (both of which, together with sterile glucose solution, happened to be at hand), and 10 cc of sterile dextrose was injected. At the end of two minutes the patient had recovered consciousness." As soon as possible, an additional 80 cc of the 20 per cent solution was introduced after a vein had been surgically exposed, immediate recovery was complete.

Protein—Protein, since 58 per cent of it is convertible into carbohydrate may also serve as antidote, therefore, in the absence of carbohydrate food the patient should quickly eat a large amount of some food high in protein content. However, Sberriil states that "though hypoglycemia may be prevented by sufficiently large quantities of protein, this influence is surprisingly feeble and by no means proportional to the theoretical value."

• 1 **Epinephrine or Pituitrin**—Epinephrine (adrenalin) is effective in combating the insulin reaction, but in undernourished individuals carbohydrate should be given with it, indeed, there would seem to be little reason to use this drug when carbohydrate is at hand for in all cases its action is quite transient and must be reinforced by the subsequent taking of glucose. The epinephrine dose is 0.5 cc in the child, and 1 cc in the adult, of the 1:1000 solution, given intramuscularly. Graham (1934) reports the effective use of pituitrin in 1-cc injection.

Calcium—Greiff (1931) reported 2 cases in which the giving of 1½ ounces (40 Gm) of calcium gluconate daily, either by mouth or in enema, was effective in overcoming insulin hypersensitivity so that a daily injection of 40 units could be resumed, Atchley *et al* employed 20 to 35 Gm of calcium chloride.

Enforced Omission of Insulin or Food—Under the wartime vicissitudes in bombed England consideration had to be given diabetics likely to be suddenly without either food or insulin. The advice of Lawrence (1940) may be briefly summarized as follows: (a) If a diabetic cannot get his usual insulin his best chance of minimizing ketosis is to continue to eat his usual carbohydrate but no fat and only a little protein, upon resuming the interrupted routine extra insulin dosage may be required to get back to the old status. (b) If a diabetic's insulin supplies are running short it would probably be fairly safe for a few days to cut dosage in half and continue the usual diet but with elimination of fat. (c) If insulin is available but carbohydrate food is not it is probably advisable as a general rule for the severe diabetic to take one-third to one-half his usual insulin without food, taking the usual meal and insulin as soon as food becomes available or the usual food and only a half dose of insulin if the preceding dose had been taken within six hours.

Insulin and Exercise.—Exercise exerts a very profound effect upon the diabetic. Even before the inauguration of the insulin era it was known that the mild diabetic was improved and the severe diabetic made worse by exercise. Nowadays exercise must always be taken into account in injecting insulin, for, other things being equal, the more exercise the less insulin will be needed, in some instances the taking of the usual dose of insulin may result in a hypoglycemic reaction if considerable exercise has preceded the

injection Many times it is possible for a golfer or an amateur gardener to eliminate a few units or an entire dose of insulin on the days when he has indulged his hobby. It has been noted also that children romping about in summer diabetic camps require less insulin than during the winter when they are less active. That the effect is not universal is emphasized however, by the study of Soskin *et al* (1934), whose 2 carefully studied patients did not show significant decreases in insulin requirements during a systematic course in physical training. Furthermore, Marble and Smith (1936) found that for exercise to exert its maximum benefit sufficient insulin must be available in the body at the time of exercise, i.e., the preferable sequence for the diabetic should be insulin, exercise and breakfast rather than exercise, insulin and breakfast.

Insulin Edema—Very few cases of insulin edema have been reported but there seems to be a clinical impression that this complication occurs not infrequently. The exact nature of the phenomenon which is not due to impaired renal or cardiac capacity and which clears up when insulin is omitted is not understood. Observers believe variously that insulin edema is a colloidal phenomenon, that insulin increases the hydration capacity of the tissue colloids of the body, that the alkali set free when insulin is given leads to water retention, that the explanation may be simply in the fact that 3 Gm. of water are retained for each gram of carbohydrate stored. Leifer's patient became edematous and gained 26 pounds in ten days then lost the edema and 12 pounds during the succeeding ten days apparently as a result of marked reduction in the salt of the diet, insulin dosage had remained practically the same. It is said that the edema can sometimes be made to disappear by dropping down with the insulin dosage and gradually building up again. If alkaline therapy is being employed it should be stopped.

Insulin Resistance—The record of insulin resistant cases—i.e., of those who either do not respond at all, or temporarily or gradually lose their ability to respond—is certainly being added to as the years go on but considering the enormous number of individuals the world over who are taking the drug, one must say that this phenomenon of insulin resistance is of very rare occurrence. A few typical cases may be instanced. Taussig's case was given as much as 1100 units in one day without becoming sugar free, after several months however, the response to insulin showed considerable improvement. Lawrence's nineteen year old patient required 400 units per day to reduce his blood sugar to normal and to keep him sugar free, the patient of Mobler and Goldburgh suddenly lost his responsiveness and died of diabetes after forty days of 437 units daily insulin dosage, upon the other hand, the patient of Karr *et al* (1933), in whom over 600 units daily did not keep the blood sugar under 200 mg. suddenly lost her resistance following the injection of a foreign protein (the serum of a rabbit that had been sensitized to a mixture of the patient's serum and insulin). In the patient of Martin *et al* the precipitating factor was apparently an allergic reaction to protamine zinc insulin, after which response to insulin was lost, there was also apparently an allergic factor in Hart and Vicens' case, Greene and Thatcher's patient was resistant to protamine zinc insulin but not to regular insulin, Wiener's patient required as much as 3250 units in twenty four hours but eight months later was controlled on 440 units daily. Mason and Sly describe the interesting case of an infant in whom glycosuria resistant to insulin could almost be stopped by

the substitution of levulose or galactose for dextrose in the diet Hendry has recorded a case in which great reduction in response to insulin was corrected by the use of thyroid substance, the patient having manifested a slight hypothyroidism, but the opposite picture is more usually seen, *i e.*, insulin resistance associated with hyperthyroidism. The possible role of suprarenal and hepatic disorders has been discussed by several authors and also the direct association of hypophyseal (pituitary) disturbance with insulin resistance. Some of the cases are in association with hemochromatosis, others with specific infections such as tuberculosis and syphilis, or with rheumatoid arthritis. All explanations of insulin refractoriness upon a single basis are still highly speculative.

In attempting to combat this unfortunate condition of course the whole gamut of possibilities must be run or at least considered. Martin *et al* (1941) say there does not seem to be any established upper limit to the number of units of insulin which may be given. Spiegelman (1940) treated 9 diabetic women with estrogenic hormone as used in the handling of the menopause (*q v*) and effected a diminution in their insulin requirement, a type of therapy which conceivably could be helpful in some cases of insulin resistance.

Insulin Allergy—Instances of insulin allergy are observed with much greater frequency than those of insulin resistance. Some of them are due to the contained animal proteins but others undoubtedly are caused by the hormone itself since skin tests to crystalline insulin are occasionally positive. The patient may apparently manifest any of the usual allergic reactions: local edema, local or general urticaria or itching rash, asthma, severe gastro-intestinal symptoms, etc., insulin resistance (see above) is also apparently associated with allergy in some instances. Insulin allergy is a very serious matter, for if the patient's diabetes cannot be controlled by diet alone, so that the use of insulin has to be continued, his condition may become a very deplorable one.

Some of the cases are arrested at once, in so far as the allergic response to insulin is concerned, by changing brands of the drug, *i e.*, changing from a brand prepared from beef pancreas to one prepared from pork pancreas, or *vice versa*, changing to crystalline insulin may also be all that is required. The several methods of attempted desensitization may be presented through representative experiences. (a) Hallermann (1930) gave 1 or 2 intracutaneous injections of 4 to 6 units of insulin and his 3 patients were able to continue use of the drug. (b) Collens *et al* (1934) gave subcutaneous doses of insulin, beginning with 0.0061 unit and gradually increasing by doubling the dose every other day, after three months both of their patients were able to tolerate 15 units twice daily, but desensitization lasted only one month. (c) Beyer (1934) using Lilly's regular insulin, known to contain both beef and pork, made up to suitable dilutions with sterile distilled water, proceeded as follows (see table opposite) in the attempt to desensitize an individual in eight hours, the treatment was successful in so far that the patient was thereafter able to use insulin though slight local and general reactions occurred at intervals. Coreoran (1938), and Ulrich *et al* (1939), have reported cases rapidly desensitized in somewhat the same manner. (d) Collens *et al* have used histamine phosphate in one case, beginning with a subcutaneous injection of 0.1 mg. and repeating the injection thrice weekly with such increasing dosage that the patient received 1 mg. on the eighth injection, and continuing at this dose to complete

the series of 13 injections. The reactions to the histamine itself were quite severe, both locally and constitutionally, but apparently desensitization to insulin was accomplished, for six months later the patient was taking 15 units daily without reaction. Roth and Rynearson (1939) have reported the successful use of histaminase (discussed in Hay Fever) in 1 case, they mention 11 other cases to which they obtained "varying results."

RAPID DESSENSITIZATION WITH LILLY'S REGULAR INSULIN (Bayer)

Units	Time	Reaction
1/100	9 15 A M	++
1/100	9 45	++
Sterile distilled water	9 47	0
1/200	10 18	+
1/200	10 40	++
1/400	11 20	++
1/1000	11 42	+
1/1000	12 20 P M	=
1/500	1 30	+
1/250	2 03	=
1/125	2 32	=
1/60	3 04	=
1/50	3 36	0
1/25	4 02	0
1/10	4 16	=
1/5	4 50	=
1/2	4 45	=
1	5 01	0
5 (hypodermically)	5 20	0

++ denotes wheal of at least 1 cm. with surrounding hyperemia + wheal of less than 5 mm. with surrounding hyperemia = no wheal, faint hyperemia 0 no reaction

A few cases of insulin allergy, be it noted, have become spontaneously desensitized. Also, there are reports of diabetes ameliorating when the patient has become allergically sensitive to insulin.

Local Fatty Changes—A few cases of extensive atrophy of subcutaneous fat following repeated insulin injections have been reported. Less extensive involvement, especially in women and children, is by no means rare—Joslin *et al.* (1940) say that this local reaction occurs in nearly 30 per cent of their diabetic children, spontaneous recovery seems usually to occur in two years but no proved method of prevention or correction has been reported. Much rarer is the development of small lipomatous growths at the site of injection. What it is that predisposes certain individuals to this reaction is also unknown.

PROTAMINE ZINC INSULIN

Advantages—A good index of the extent to which protamine zinc insulin has replaced regular insulin is obtained in the statement of Joslin *et al.* (1940) that practically all of their patients who require insulin are obtaining it in this form. The outstanding advantages of this new agent are the following: (a) Only one injection need be given per day because the drug has a remarkable constancy of action, i.e., when given in the day-by-day treatment of diabetes it furnishes a continuous and relatively even supply of insulin from the subcutaneous depots. Once fully established, the action, as recently shown by Ricketts (1941) is maximal at all times, thus enabling the patient to take his injections at whatever time is most convenient, provided they are spaced

twenty four hours apart (b) The blood sugar level during fasting is set at a certain level by this drug the height depending upon the dose. The blood sugar is pushed above this level by food during the day and gradually returns to it when the patient is without food during the night, nocturnal hypoglycemia does not indicate a greater action during the night but merely that the dose used is setting the basic level too low (c) The patient's nervous tension is greatly lessened because meals need not be taken absolutely on schedule (d) Mosenthal and Mark (1941), finding tuberculosis prognosis at Sea View Hospital distinctly more favorable in patients treated with this drug than with regular insulin, say they share the general impression (it is still no more than an impression) that ketonuria, diabetic coma and gangrene and infection of the lower extremities occur less frequently since protamine zinc insulin has become generally used.

I think it a fact of great practical interest that under the conditions of air siege in England, protamine zinc insulin is being preferred (Brit Med Jour, Feb 8, 1941) because it is easier to take carbohydrates to shelters and shops than to give additional insulin injections there.

Disadvantages—(a) If enough protamine zinc insulin is given to maintain a severe diabetic sugar free for twenty four hours of the day the patient is hypoglycemic much of the time (b) We do not know that prolonged hypoglycemia does not cause permanent brain and liver damage (c) Hypoglycemic reactions under protamine come on more gradually usually than under regular insulin and are more difficult to recognize since such symptoms as headache, nausea and vomiting may cause confusion with impending coma, drowsiness, restlessness and crossness, and paresthesias may also occur as well as the more usual symptoms of sweating, tremor, hollow hunger, etc (d) There is sometimes a hyperglycemic rebound from prolonged hypoglycemia, and it is not certain that this should not be taken as evidence that the system is taking severe punishment, Herold (1940) has specially stressed this point recently (e) Local reactions of an annoying nature sometimes occur with this agent, but the incidence of these reactions is lessened almost to the vanishing point if alcohol is not used to sterilize the injection outfit and especially if the injections are given deeply beneath the skin, it is best to pinch up the skin and then inject at right angles into the triangle thus formed.

Practical Use.—The undoubtedly great advantages of protamine zinc insulin may be enjoyed, and its serious disadvantages appreciably discounted by the employment of several compromise measures. I am presenting the practical features of the newer approaches to the problem under three heads, as follows (a) the use of protamine plus regular insulin, (b) readjustment of the diet, (c) relative disregard of sugar. Either one of these types of therapy will succeed in many cases and perhaps none of them in all, in our present state of knowledge the reader will do well to suit his approach to his individual case.

Protamine plus Regular Insulin—Most patients with mild diabetes requiring no more than 20 units of protamine zinc insulin may usually inject this amount all in one dose before breakfast—the time which seems most convenient for the majority of individuals—and obtain satisfactory control without hypoglycemia as a constant threat. But when larger doses are required it usually happens that if sufficient is given before breakfast to keep the blood sugar normal throughout the day the patient is extremely liable to hypo

glycemic reactions in the early hours of the morning. Of course one could give a smaller dose of protamine and then inject some regular insulin before each meal to take care of the postprandial rise in blood sugar, but in such a practice it is difficult to see that anything is gained by using the protamine at all. Most men compromise by giving an amount of protamine calculated to keep the blood sugar normal after it begins to become operative and combining with it in the morning an injection of a small amount of insulin to take care of the rise after breakfast before protamine effect has fully developed. One should know rather exactly what is going on in the patient, however, before adopting this measure. I summarize Mosenthal and Mark's (1939) observations: (a) If the rising urine contains more than 0.1 per cent sugar, the blood sugar during the night has probably been above normal and one may consider increasing protamine dosage, if the rising urine contains no sugar, blood sugar may have been relatively normal in the night or too low and investigation should be made regarding any slightest evidences of hypoglycemic reaction in the early morning hours looking toward reduction of protamine dosage. (b) Blood sugar determination at about 6 A.M. would be ideal but this is seldom possible. An elevated blood sugar one-half to several hours after breakfast, the time at which specimens are usually taken, may be regarded as indicating that the protamine dosage alone is not sufficient, provided the patient has not had evidences of hypoglycemia in the earlier hours, in which case the present high blood sugar may be only the hyperglycemic rebound from an extremely low early morning blood sugar. (c) In the event that the protamine dosage is not causing hypoglycemia in the night and is taking care of the blood sugar during the day except for postprandial rises, a single dose of regular insulin with the protamine in the morning is likely to take care of the situation.

Regarding dosage, it is usually stated that less protamine than regular insulin is required, but this must of course vary greatly with cases and the amount of control desired. Mosenthal and Mark limit their dosage to 40 at most 50, units of protamine, supplementing with regular insulin if this amount does not suffice. As to supplementary regular insulin dosage, they advise the giving of only 4 to 6 units initially and raising carefully by 2 unit increments. Such studies as that of Watsoo (1940) indicate that it is not advisable to mix the two insulins before injecting or to inject them from separate syringes through the same needle unless the needle is replaced in the subcutaneous tissues, the regular insulin is converted into protamine insulin by contact with the latter. However, Ulrich (1941) has recently denied that this is so—obviously more experience is needed to indicate where the truth lies.

Readjustment of Diet—This approach is based upon the hypothesis that if the single dose of protamine required to maintain the desired control keeps the patient upon a hypoglycemic level at various times during the day and makes him extremely liable to severe hypoglycemic reactions during the early hours of the morning, the thing to do is supply additional carbohydrates at frequent intervals through the day and especially late at night. Several plans have been adopted, as follows:

LATE PROTEIN—Pollack and Dolger (1938) reported good success by availing themselves of the fact that protein slowly yields about 80 per cent of itself as carbohydrate, they simply instructed their patients, after a preliminary careful quantitative study in 40 individuals, to take half or more of

their daily protein allowance at the evening meal in order to buffer the tendency toward dangerous degrees of hypoglycemia during the night

EATING BETWEEN MEALS—The plan of Collens and Boas (1939) stresses what they like to call "intercibal feedings," i.e., the taking of food at 10 A.M., at 3 or 4 P.M. and again very late at night, this in addition to the usual three meals. The plan, with regard to distribution of carbohydrate, follows

TIME	MEAL	PER CENT OF TOTAL CARBOHYDRATE IN 24 HOURS
8 A.M.	Breakfast	25
10 A.M.	Intercibal feeding	7
12 noon	Lunch	25
3-4 P.M.	Intercibal feeding	7
6 P.M. (later if possible)	Dinner	20
11-12 P.M.	Postcibal feeding	15

These intercibal feedings are not more than snacks such as a small amount of fruit juice, though the last one at night should also contain some protein from which carbohydrate will become slowly available

THE FOUR MEAL DAY—Margolis and Lieinstein (1940) record results with which they are highly pleased, their only departure consisting in re planning the patient's schedule on a four meal basis. The caloric division is as follows: $\frac{1}{2}$ of the total caloric intake at 8 A.M., $\frac{1}{4}$ at noon, $\frac{1}{4}$ at 5 P.M., $\frac{1}{4}$ at 9.30 P.M. In some instances the last meal has contained the $\frac{3}{4}$ portion if necessary. They report several cases in which single morning doses of 50 to 80 units of protamine have been handled on this regime without reactions and without the supplementary employment of regular insulin

Relative Disregard of Sugar—This plan of treatment involves a very wide departure from previously accepted practice in that it does not look upon absence of glycosuria and a constantly normal level of blood sugar as the true gauge of successful treatment. It is based rather on the assumption that if a patient receiving moderate doses of protamine zinc insulin daily can take a high carbohydrate low fat diet, maintain his weight, be in nitrogen equilibrium (i.e., not have tissue proteins consumed during the night to obtain carbohydrate), excrete no ketone bodies in the urine, and be absolutely free from symptoms it does not greatly matter if he has a more or less constant hyperglycemia and even glycosuria. Mosenthal and Mark (1941) have recently pointed out that the first of the traditional viewpoints was surrendered when it was acknowledged that an elevation of blood sugar in the absence of glycosuria is not only harmless but even beneficial, because hyperglycemia promotes the utilization of sugar, does not predispose to infections or cause degenerative changes in the tissues, and is in fact the rule in elderly (non-diabetic) individuals. Now we have gone even further and decided (some of us, that is, for the point is still highly controversial) that even glycosuria, under the conditions above stated, is not harmful. The foremost exponents of a therapy based upon these premises are Tolstoi and Weber (1940). At the time of their report they had treated 84 patients without an attempt to "desugarize." Many of these patients achieved a sugar free state on the single dose of protamine but there were 27 who continued to reveal various quantities of sugar in their urine for a year or longer. Very rarely because of a slight

cold or without any obvious cause a slight trace of acetone would appear in the urine, but this was said never to be of any consequence as it usually yielded to the administration of two $7\frac{1}{2}$ grain (0.5 Gm) tablets of sodium chloride at two hour intervals with a glass of water for each dose, when the acetone persisted or increased, one or two small doses of regular insulin were given until the urine was free of acetone again. All the patients were of the clinic type, at work and glad to be relieved of careful dietary measurements. This type of treatment, offering all the advantages it does, is certain to have an extensive trial. Even before the paper of Tolstoi and Weber, who are at Cornell, appeared Bridge and Winter (1939) had concluded from their studies of the effect of insulin on diabetics, at Johns Hopkins that neither the value for blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes.

NEW INSULINS

Crystalline zinc insulin has been favorably reported upon several times as lying in its action somewhere between regular insulin and protamine zinc insulin, but there are reports of carefully performed studies by Ricketts and Wilder (1939), Marble and Vartiainen (1939), and Jackson *et al* (1940) indicating that any alleged differences from regular insulin are certainly not consistently obtainable. The product has not been Council accepted. Bauman (1940) has reported a few cases treated with *globin insulin*, as have also Bailey and Marble (1942), Feinblatt (1940) has studied *hexomine insulin* and Bailey and Marble *histone zinc insulin*. All of these latter drugs are still in the experimental stage.

KETOSIS AND COMA

When the ketone bodies begin to build up in the blood as a result of deficient carbohydrate metabolism, the kidneys excrete acids in the free form and also as ammonium salts, furthermore some of the bicarbonates of the blood are split up to yield base for neutralizing purposes, the liberated CO_2 being eliminated by the lungs. When these mechanisms alone fail to keep pace with the production of acids the fixed bases begin to be called upon and the body loses sodium—since this latter step really amounts to a decrease in total salt concentration there results a state of dehydration because water is excreted to maintain isotonicity in the tissues. Hence the patient is acidotic (due to the ketone bodies in the blood), hyperpneic (the liberated CO_2 must be eliminated), and dehydrated (because of the sodium chloride loss). The very obvious aims of treatment therefore, should be to put a stop to the defective utilization of carbohydrate and to replace the carbohydrate, fluid and salt that have been lost. In short, give insulin, dextrose and saline solution. It seems to me now to be the opinion of practically all the leaders in diabetes therapy that the additional routine administration of alkalis is unnecessary since it is specifically sodium that has been lost and this is being replaced in the sodium chloride solution administered—for example, Campbell *et al* (1940) say that the policy at the Mayo Clinic nowadays is to give 250 to 500 cc of 5 per cent sodium bicarbonate solution intravenously only in critical instances in which there has been failure of response to the above corrective and replacement therapy.

Insulin, Dextrose, Saline—In a series of studies since 1937, it seems to me that Rahinowitch, Fowler and Bensley, of Montreal, have established the

value of their type of therapy, which consists in administering all the insulin that is likely to be necessary at one time in the beginning, using both regular insulin and protamine zinc insulin, and then giving large amounts of dextrose as long as required. With increasing experience they have decided that the best insulin dosage is the following: all injections to be given as early simultaneously as possible: 100 units of regular insulin intravenously, 100 units of regular insulin subcutaneously, for effect which will come on after the rapid action of that given intravenously has begun to disappear, and 200 units of protamine zinc insulin subcutaneously for its well known delayed but prolonged action. Dextrose is got into the patient by any channel possible and in large amounts—the average total amount given patients in their series of 11 cases on whom very detailed data are published was about 780 Gm. in about 40 hours. The three very apparent advantages of this type of treatment are: (a) the initial amount of insulin employed is large which is

TABLE 11.—INSULIN-DEXTRASE-SALT SOLUTION IN DIABETIC COMA
(Barack)

Degree of coma	Total insulin units	Protamine subcutaneously	Regular intravenously	Regular subcutaneously	Dextrose grams		Salt solution cc per day
					Per hour	Per day	
Mild	100	50	25	25	10	200	1000
Moderate	200	100	50	50	20	400	2000
Severe	300	150	75	75	30	600	3000
Profound	400	200	100	100	40	800	3000

1 After admission take blood for analysis. Give the three doses of insulin at once.

2 Insulin for subcutaneous use should be divided into 3 or 4 portions and injected into different sites for better absorption.

3 Dextrose is given hourly as per schedule by mouth, gavage, skin or vein.

4 Gastric lavage, enema and external warmth when necessary.

in accord with all current practice, (b) the method of giving the insulin insures not only an immediate but a steady and prolonged action, (c) and the use of large amounts of carbohydrate in the presence of all this insulin not only induces rapid reduction of ketosis but permits the storage of glycogen to take place and thus lessens the likelihood of an early reversion to the ketotic state. That the dextrose is being utilized as above indicated is shown by the fact that in their series though the average blood sugar before treatment was 612 mg. per cent, it was reduced to 165 mg. per cent in an average period of five and one half hours, and in spite of the administration of an average of about 780 Gm. of sugar during about 40 hours, the average amount in the urine was only about 52 Gm., in short, an average of 728 Gm. was retained and utilized in the body. Another advantage of this method of treatment, not quite so obvious as the above but nevertheless very important, is that the administration of all this carbohydrate prevents hypoglycemic reactions as

ketosis is overcome. In Rahinowitch's cases there have been no reactions even when the blood sugar level has fallen very low and remained there several hours, which supports the widely accepted view that the neurological manifestations of insulin hypoglycemia are not due to lowering of the sugar content of the blood but to reduction of the sugar content of the brain.

Of course this treatment is employed in conjunction with the use of large amounts of saline. Barach's (1940) method of systematizing the therapy is shown in the accompanying chart, from which it will be seen that the patient receiving 400 units of insulin is given 40 Gm. of dextrose per hour (a total of 800 Gm. for the day) and also 3000 cc. of physiologic saline solution. The distinction between mild, moderate, severe and profound cases is difficult to make and I shall certainly not attempt it here, it seems well worth repeating that Rahinowitch and his associates now prefer the highest insulin dextrose dosage—that designated for "profound" cases in Barach's chart (Table 11)—as practically routine therapy in all cases. To be sure, in an occasional case additional insulin may even have to be given, usually in the form of supplementary injections of regular insulin, sometimes saline must also be given in quantities enormously greater than shown in Barach's chart.

Lavage, Cleansing Enema and Warmth—In most hospitals, lavage of the stomach is employed routinely nowadays as soon as beginning coma is diagnosed, time has shown the procedure to be of great value, for a dilated or partially filled stomach is a great handicap to one who during the succeeding twenty-four hours must grapple catch as catch-can with death, 200 to 300 cc. of saline solution can be left in the stomach after the washings come away clear. Ordinarily a saline cleansing enema should be given as soon as possible. Of course the patient should be kept warm by all the devices usually employed in treating a case of shock—nearly all of these patients have a subnormal temperature at the beginning of coma, and an individual with subnormal temperature is not well armed for a fight.

Circulatory Stimulation—A patient not improved by judicious application of the methods discussed above is not likely to benefit from the employment of such stimulants as epinephrine, ephedrine, metrazol, coramine, etc. Joslin *et al.* (1940) say they have encountered no case in which such drugs appeared to be life saving.

TREATMENT OF COMPLICATIONS.

Intercurrent Infection—It is well known that an acute intercurrent infection makes a diabetic worse, but it does not seem to make him permanently worse. Lawrence and McCance have suggested that the harmful effect of an infection is to be explained by the neutralization of the power of the insulin through stimulation of the thyroid and suprarenal glands, but there is likely more to the matter than simply this, for example, the theoretical possibilities of increased destruction of insulin as well as decreased production of it in the pancreas, or an interference with glycogen storage in muscles and liver, furthermore, Rahinowitch suggests that an insulin destroying enzyme may be present during infection. If the infection is local, prompt surgical drainage is indicated (Rosenthal and Behrendt found that if fresh pus is mixed with insulin and injected into rabbits the influence of the insulin is abolished), if general, it must be recognized that the fever will cause an increase in metabolism and thus bring ketosis nearer

I think that most men will now agree with Duncan (1939) when he says that diabetic control can be maintained in the presence of even very severe complicating infections if the diet is divided into 6 equal feedings spaced at four hour intervals throughout the twenty four hours, giving one sixth the total insulin dosage before each feeding and basing the amount of insulin used upon the sugar content of a specimen of urine obtained if possible before each feeding. As a practical matter, with such frequent feedings and insulin dosings, one blood sugar determination in the twenty four hours will suffice as an index of the level. In milder infections, only 4 feedings and 4 insulin dosings may be needed, but whether the 4- or the 6-feeding routine is adopted it must be adhered to with absolute rigidity if successful control is to be expected. Duncan feels that the use of protamine zinc insulin during these acute complications is confusing and detracts from the simplicity of the program, he therefore uses only regular insulin until the emergency has passed. However, Joslin *et al* (1940) continue protamine zinc insulin in a patient who has been taking it and supplement it at four- to six hour intervals with regular insulin in the following dosage according to the color reaction of the urine: red, 10 units, orange, 8 units, yellow, 6 units, yellow green 4 units, if regular insulin is being depended upon alone the above doses are doubled.

Chemotherapeutic agents such as the arsineals and sulfonamides, may be employed in the diabetic just as in the nondiabetic. Baldwin and Root (1940), discussing urinary tract infections, also speak of the free use of ammonium mandelate and methenamine (urotropin) and also ammonium chloride as an acidifying agent.

Tuberculosis is no longer looked upon as making prognosis hopeless, and Humsforth (1938) very optimistically concludes from his studies that treated diabetics are no more likely to develop tuberculosis than nondiabetic subjects. McKean *et al* (1941) feel that mortality in cases of associated diabetes and tuberculosis parallels closely that of tuberculosis alone. Root and Bloor (1939) point out that diabetic patients make excellent subjects for pneumothorax and thoracoplasty.

Syphilis in association with diabetes was studied by McDaniel *et al* (1940) in 258 patients, they concluded that syphilis does not seem to alter the type of diabetes and that it may be treated just as it would be in a nondiabetic individual.

Gastro-intestinal Disturbances—Acute gastro intestinal upsets are dangerous because if the patient cannot eat, or vomits what he does manage to get down, he is being deprived of carbohydrate and hence approaching closer to ketosis, insulin should not be omitted but only cut down somewhat in dosage and as careful watch as possible be kept on the levels of sugar in the blood and urine. Diarrhea is also a serious matter because it also robs the patient of food and fluids. Here again the result may be ketosis or it may be hypoglycemia, the former if the deprivation of carbohydrate causes the breakdown of body tissues, just as in the case of vomiting and inability to eat, the latter because the low state of metabolic activity of the body may render insulin relatively hyperactive. In any case the chief thing to be desired is to get food into and absorbed by the patient, covering with insulin of course, individualization of treatment is absolutely necessary.

Cardiovascular Complications—The majority of the foremost students of

diabetes agree that in arteriosclerotic, hypertensive, peripheral vascular, or coronary disturbances insulin should be employed with great caution, since sudden lowering of the blood sugar level seems to be particularly difficult for such diabetics to combat. True anginal pain subsequent to insulin injection has been several times reported even in patients not previously having had such attacks.

Neurologic Complications—Jordan (1936), in studying Joslin's material found that he could separate the surprisingly large number of cases with neurologic complications into three types: (a) hyperglycemic, (b) degenerative, and (c) neuritic. Patients in the hyperglycemic group are characterized by neuritic symptoms but with hardly any objective signs. They seem all to be relieved within a few days when the diabetes is brought under control by proper treatment. In the second and third groups there are diverse manifestations of neuropathology on a degenerative basis with or without neuritic accompaniment, and always with arteriosclerosis. Though some of these patients improve, it seems that most do not, and I make out from the report that the particular factors at fault have not been discovered as yet. The fact stands out, however, that persistent treatment of the diabetes is indicated in all cases. It is also well worth noting that Fein *et al.* (1940) have described 9 cases of symmetrical peripheral neuropathy in diabetic patients having proved vitamin B₁ deficiency; these cases all responded to thiamine therapy (methods in Beriberi).

Sandstead and Beams (1938) have studied 13 patients with pains classified as of neuritic origin in 10 and of vascular origin in 3. The pain had persisted in spite of treatment for the diabetes but in all instances was markedly or completely relieved upon the oral administration daily of 0.25 to 0.5 Gm. of sodium chloride per Kg. body weight, which the authors rationalized as probably indicating that ischemia was the underlying factor resulting in pain.

Eye Complications—The principal ocular complications are: (1) transient changes in refraction, which are unimportant and apparently occur as frequently with as without insulin; (2) diabetic cataract, which seems to have decreased in incidence since insulin came into use; (3) lipemia retinalis, which is now rarely seen; (4) toxic amblyopia, which has also much decreased under careful insulin management; and (5) diabetic retinitis. This latter involvement has apparently become more prominent under the new type of treatment, probably largely if not solely because more diabetics are living into the arteriosclerotic age. So far it has not been conclusively demonstrated whether high carbohydrate, low fat and liberal insulin therapy has served to control the progress of this serious complication. The especially interested reader will find both Reese's (1935) and Wagener's (1936) reviews listed in the Bibliography.

Pruritus and Furunculosis—These two dermatoses are frequent complications in diabetes, the former always very annoying, the latter often very serious. Their treatment is described in the chapter on skin diseases.

Vitamin Deficiencies—A careful study of the literature of vitamin therapy in diabetes leaves the following clear impressions: (a) there are no vitamin deficiencies characteristically associated with diabetes; (b) employment of vitamins in therapy in well controlled diabetics on adequate diets with insulin is not beneficial so far as the diabetes *per se* is concerned; (c)

vitamin deficiencies occurring concomitantly with diabetes will respond to vitamin replacement therapy just as in instances not complicated by diabetes

SURGERY IN DIABETES

Since the advent of insulin, surgical diabetic mortality has been considerably lowered, but it is still several times that of nonsurgical diabetes. Gangrene and carbuncle are the principal dealers of death. The general practitioner must be ever watchful for early signs of impaired circulation in the extremities: claudication, coldness, pain, numbness, diminished arterial pulsation, rose spots, hlebs, scars. And of course he must enjoin upon his patients the necessity for utmost cleanliness of the body, particularly the feet, and the avoidance of trauma, and instant serious attention to local infections, even of the slightest. Blotner's (1936) warning that excessive smoking may predispose to diabetic gangrene should not be overlooked.

The choice of anesthetic, and the treatment of gangrene and carbuncle, are of course purely surgical matters, so also to some extent are the preoperative and postoperative care of the patient, but I think it will not be presumptuous to say two words here regarding these latter matters.

Preoperative Care—If the patient is under good diabetic control and is coming up for an elective operation, the only preliminary alteration in surgical orders usually necessary is to have him given 6 to 10 ounces of orange juice and 10 to 20 units of insulin two hours before operation, adding 10 Gm. of dextrose intravenously with another 5 units of insulin just before or during the operation if the CO_2 -combining power of the plasma is less than 40 volumes per cent. If the patient is not under diabetic control, or if the operation is of an emergency nature or complicated by infection, the treatment had better be that of acidosis with threatened coma. The diabetic coming to operation for the relief of a complicating hyperthyroidism had best be treated as though his diabetes is complicated by infection, for hyperthyroidism like infection decreases the power of insulin, with the relief of the hyperthyroid state the severity of the diabetes is nearly always much ameliorated.

Postoperative Care—The total amount of insulin which the patient has been taking preoperatively in twenty-four hours should be given in the twenty-four hours succeeding operation, with this difference only that it is best to divide it into smaller portions and inject every three or four hours, during the twenty-four hours the patient should receive in the form of intravenously administered dextrose the amount of carbohydrate customarily allowed in his diet. Thereafter, dietary readjustment must be made, bearing in mind that the patient not infrequently after operation requires for a while somewhat different insulin dosage than before. The appearance of sugar in the urine at any time shortly after operation, or the signs of hypoglycemia or acidosis, of course require complete accommodation of the treatment to the new conditions.

It will be extremely interesting to see what the effect of the newest type of routine diabetic therapy, that which I have earlier called the "relative disregard of sugar" treatment, is going to have on the postoperative treatment of diabetics. Greene *et al.* (1940) have already concluded that the incidence of delayed healing and of infection of originally clean wounds bears no relationship to the height of the blood sugar or the amount of glycosuria.

DIABETES IN CHILDREN

The advent of insulin made it possible to treat childhood diabetes with as good success as adult diabetes, the new high carbohydrate low fat diets have amplified the problem and much eased the parental burden. I think that the reader will find the practical methods of therapy, discussed earlier in this chapter, as applicable to one age as another. The following points which are really not variants of that method, are perhaps worth listing.

Insulin and Protamine Zinc Insulin—Practically all childhood cases are relatively severe. Insulin requirements are also higher than for an adult with diabetes of comparable grade, but there is no definite proportional gauge and therefore dosage must be evolved according to the needs of the individual patient. The approach of puberty, especially in girls, often accentuates this difference between childhood and adult utilization of the drug. After sexual maturity has become established reduction in dosage is usually possible.

Protamine zinc insulin is being used by all leaders in diabetic therapy with fully as good results in children as in adults. It is interesting that several physicians in Sweden and Germany had begun before the outbreak of World War II to use "free" diets in their children, i. e. allowing the child to eat what it wanted and giving enough insulin to prevent ketosis but disregarding slight to moderate hyperglycemia and glycosuria. In short before the type of protamine zinc insulin therapy which I have earlier described as "relative disregard of sugar" was instituted, trials of much the same sort were already being made with regular insulin (see Lichtenstein 1938, in Bibliography).

Exercise—Proper management comprises full utilization of the insulin sparing function of exercise, but with the greater lability of childhood metabolic processes the omission of exercise at accustomed times is more dangerous than in adults. Setting up exercises of definite type and duration have been shown to be well worth instituting during those seasons when spontaneous outdoor exercise is restricted or for routine performance throughout the year by children not temperamentally disposed to be very active. It is well to bear in mind that if the child's treatment is standardized during a preliminary period in hospital, he will require to have his insulin dosage reduced when he returns to normal play activity at home.

Infection—The effect of infection in reducing insulin efficiency is much *more rapid and more marked in children than in adults*. A child completely free of glycosuria, hyperglycemia and acidosis one day may be in coma the next as a result of even the milder sort of acute infectious process.

Acidosis, Coma and Hypoglycemia—As just stated, the transition from a state of complete control to one of coma may be extremely rapid, a food orgy, or the omission of a dose of insulin, can institute it as rapidly as the onset of infection. Similarly, the omission of a meal, a bout of vomiting, or excessive indulgence in exercise may precipitate hypoglycemic shock quite suddenly. Unfortunately, the prodromal symptoms of either of these opposite states are less typical in children than in adults, therefore any unusual behavior of a diabetic child, such as unwonted irritability, obstinacy, rage, pallor, tearfulness, hunger, drowsiness, etc., should be quickly analyzed to determine its possible relationship to a sin of omission or commission. Some physicians feeling that the symptoms of impending shock form a pattern which is typical for each individual, like deliberately to induce such an experience for educative

purposes during the early period of diabetic training, however, that the identical prodromata always appear is denied by many observers

EFFECT OF PREGNANCY UPON DIABETES

Insulin has unquestionably increased the fertility of diabetic women and it is now the consensus that the fact of pregnancy itself offers hardly any threat to the life of the diabetic woman provided she is in the hands of a physician who thoroughly understands the treatment of diabetes and is herself fully cooperative. But the sudden changes in tolerance, implying necessarily dietary and insulin adjustments, are unpredictable. Nor will a woman always react similarly in each pregnancy. Northmann (1941) reports a patient whose first pregnancy terminated in coma whereas during the course of the second pregnancy there was a remarkable improvement in carbohydrate utilization. In a word, the physician must be more than usually on the *qui vive* in handling these cases, but treatment itself does not vary in principle from that of the nonpregnant diabetic (but see Hormonal Therapy below).

Nausea and vomiting during the first trimester demand readjustments so that adequate carbohydrate is kept burning to prevent ketosis. Joslin *et al* (1940) say this condition can best be handled by hourly feedings and the administration of insulin every three hours, supplementary use of intravenous dextrose to be made if necessary, or if the patient has been on protamine zinc insulin this may be continued and regular insulin used at noon and at 6 P.M. as indicated by tests.

Prolonged difficult labor which occurs more frequently among diabetic than nondiabetic women because of the overweight of the child centers attention upon the actual period of labor as the most trying from the diabetic standpoint. Not only is there the possibility of a plunge into hypoglycemic shock upon the one hand or ketosis and coma upon the other, but the possibilities of perineal or cervical tears and of postpartum sepsis are undoubtedly greater causes for concern in the diabetic than in the nondiabetic woman. Many observers have felt that cesarean section at about the thirty-sixth to thirty-seventh week is indicated in most instances but the opinion is not unanimously held, for example, White, of Joslin's group, formerly advocated section but is now not certain apparently that it has had a favorable effect upon the outcome of pregnancy. Mengert and Laughlin (1939) report 33 pregnancies in diabetic women with 28 spontaneous deliveries, 2 breech extractions and only 1 cesarean section all the operative deliveries being performed because of obstetric indications only.

Diabetic women are seldom able to nurse their infants. Kramer (1935), however, stresses the point that when lactation begins one should be on guard against a blood sugar drop necessitating reduction in insulin dosage.

Effect of Diabetes upon the Infant—The studies of White (1940) and the Joslin group show that fetal mortality in the pre-insulin era was 44 per cent and that in the present insulin era it is 33 per cent. About 40 per cent of these deaths are due to early spontaneous abortions and 60 per cent to late occurrences, i.e., stillbirths and death in the first few hours after delivery, the latter apparently due to asphyxia, cerebral edema, hypoglycemia caused by overfunction of the infant's own pancreas, or a much reduced alkali reserve.

Hormonal Therapy During Pregnancy—As a result of her studies in Joslin's clinic, White (1941) now believes that the accidents seen in diabetic pregnancies are not due to imperfectly controlled diabetes but to hormonal imbalance, as follows (a) In some instances in the pregnant diabetic the serum prolactin rises to abnormal heights for reasons still unknown, (b) One defense mechanism against this state of affairs is destruction of the offending placenta and incidentally the child, thus accounting for the high incidence of stillbirth, (c) The other defense mechanism consists in expulsion of the placenta and the child, accounting for the high incidence of miscarriage. White originally had her attention drawn to the necessity to seek some explanation of these matters outside the diabetic state *per se* by the observation that in many diabetic women the course of pregnancy was uneventful until about the sixth month, but that at any time thereafter there often developed a sudden toxic state—edema, albuminuria, rising blood pressure—which promptly disappeared with the death of the fetus. Her present policy is to administer stilbestrol by mouth in doses of 40 to 120 mg daily and pregnolone 10 to 40 mg daily, in cases in which the serum prolactin is found to be higher than normal in studies which are begun as near the twenty-fourth week as possible. Her series of cases is still small but the findings seem to her apparently to Joslin (1941) also, very significant. (a) Among 12 consecutive untreated patients with abnormal prolactin levels the fetal survival was 42 per cent, (b) Among 35 abnormal but treated patients 89 per cent, (c) Among 35 normal (*i.e.* no prolactin rise) and therefore untreated patients 91 per cent. This work has not yet been confirmed by any other groups of workers and it has been severely criticized by Hurwitz (1941) who is able to show about the same results without hormone therapy, but it is an interesting new approach and bears watching.

Treatment of the Newborn Infant—Randall and Rynearson (1930) fearing a state of hypoglycemia in the infant due to overfunction of its pancreas, place the child in an atmosphere of 40 to 50 per cent oxygen in an incubator and inject 5 cc of 10 per cent dextrose solution into each buttock, repeating 10-cc doses at such intervals as are dictated by the blood sugar level, the behavior of the infant, and its ability to take food by mouth. Beginning within four hours if possible 10 cc of dextrose solution, or 7 cc of lactic acid karo mixture (see below), is given every two hours for the first forty-eight hours *if tolerated, thereafter, 30 cc of the mixture every three hours but whenever* it is poorly taken or behavior indicates hypoglycemia, resort is had again to the intramuscular introduction of dextrose. Mixture using sterilized utensils mix 70 Gm karo syrup and 930 cc whole milk and boil fifteen minutes, cool until ice cold and add 120 drops of 85 per cent lactic acid solution, drop by drop while stirring, do not warm too much for feeding, or the mixture may curdle.

I think it should be noted that the more recent studies of Hartmann and Jandon (1937), Miller and Ross (1940), and Sisson (1940) cast some doubt upon the significance of the hypoglycemia in these infants since the blood sugar level is apparently often low in infants born to nondiabetic mothers. Sisson goes so far as to say that hypoglycemia of an abnormal degree is a rare occurrence in the infants of diabetic mothers unless insulin has been given the mother shortly before delivery.

TABLE 12 —FOR COMPUTATION OF DIABETIC DIET (BARACH)

(Part I)

Add or subtract the pounds designated if patient is a female

Normal Weight—Six Months to Seventeen Years

Height	Age	Weight.	
		Male	Female
26 in.	6 mos.	18 — 2 lbs.	
27 in.	8 mos.	20 — 2 lbs.	
28 in.	10 mos.	21 — 2 lbs.	
29 in.	1 yr.	22 — 2 lbs.	
32 in.	1½ yrs.	25 — 2 lbs.	
34 in.	2 yrs.	27 — 1 lb.	
35 in.	2½ yrs.	30 — 2 lbs.	
37 in.	3 yrs.	32 — 2 lbs.	
38 in.	3½ yrs.	34 — 2 lbs.	
39 in.	4 yrs.	36 — 2 lbs.	
40 in.	5-7 yrs.	38 — 1 lb.	
42 in.	5-8 yrs.	42 — 1 lb.	
44 in.	5-8 yrs.	46 — 1 lb.	
46 in.	5-9 yrs.	50 — 2 lbs.	
48 in.	6-11 yrs.	54 — 2 lbs.	
50 in.	7-12 yrs.	58 — 1 lb.	
52 in.	7-12 yrs.	62 — 2 lbs.	
54 in.	8-13 yrs.	70 — 2 lbs.	
56 in.	9-14 yrs.	78 — 2 lbs.	
58 in.	10-16 yrs.	86 + 2 lbs.	
60 in.	10-17 yrs.	96 + 4 lbs.	

Normal Weight—Seventeen to Thirty-four Years

Ages Height	17 to 19		20 to 24		25 to 29		30 to 34	
	M	F	M	F	M	F	M	F
4' 10"	109 — 1		115 — 4		120 — 6		125 — 6	
4' 11"	111 — 1		117 — 4		122 — 6		125 — 6	
5' 0"	113 — 1		119 — 4		124 — 6		127 — 6	
5' 1"	115 — 1		121 — 4		126 — 6		129 — 6	
5' 2"	118 — 1		124 — 4		128 — 6		131 — 6	
5' 3"	121 — 1		127 — 4		131 — 5		134 — 6	
5' 4"	124 — 1		131 — 5		134 — 5		137 — 5	
5' 5"	123 — 2		133 — 6		138 — 6		141 — 5	
5' 6"	132 — 2		139 — 6		142 — 6		143 — 5	
5' 7"	136 — 2		142 — 6		146 — 6		149 — 5	
5' 8"	140 — 2		146 — 5		150 — 6		154 — 6	
5' 9"	144 — 3		150 — 5		154 — 6		158 — 6	
5' 10"	148 — 3		154 — 5		158 — 6		163 — 8	
5' 11"	153 — 3		158 — 5		163 — 8		168 — 10	
6' 0"	158 — 3		163 — 6		169 — 10		174 — 12	
6' 1"	163 — 3		168 — 6		175 — 12		180 — 14	

Normal Weight—Thirty-four to Fifty-four Years

Ages Height	34 to 39		40 to 44		45 to 49		50 to 54	
	M	F	M	F	M	F	M	F
4' 10"	125 — 5		128 — 4		130 — 3		131 — 2	
4' 11"	127 — 5		130 — 4		132 — 3		133 — 2	
5' 0"	129 — 5		132 — 4		134 — 3		135 — 2	
5' 1"	131 — 5		134 — 4		136 — 3		137 — 2	
5' 2"	133 — 4		136 — 3		138 — 2		139 — 1	
5' 3"	136 — 4		139 — 3		141 — 2		142 — 1	
5' 4"	140 — 4		142 — 3		144 — 2		145 — 1	
5' 5"	144 — 4		146 — 3		148 — 2		149 — 1	
5' 6"	148 — 4		150 — 3		152 — 1		153 — 1	
5' 7"	152 — 4		154 — 3		156 — 1		157 — 0	
5' 8"	157 — 5		158 — 4		161 — 2		162 — 0	
5' 9"	162 — 6		164 — 5		166 — 3		167 — 1	
5' 10"	167 — 8		169 — 7		171 — 5		172 — 2	
5' 11"	172 — 10		175 — 9		177 — 7		178 — 4	
6' 0"	178 — 13		181 — 12		183 — 10		184 — 7	
6' 1"	184 — 16		187 — 15		190 — 13		191 — 10	

TABLE 12 (Continued)

(Part II)

Conversion Table

2.2 lbs = 1 Kilo

Body weight		Body weight		Body weight	
Lbs	Kilo	Lbs	Kilo	Lbs	Kilo
15.4	7	83.0	38	151.8	69
17.0	8	85.8	39	154.0	70
19.8	9	88.0	40	156.2	71
22.0	10	90.2	41	158.4	72
24.2	11	92.4	42	160.6	73
26.4	12	94.6	43	162.8	74
28.6	13	96.8	44	165.0	75
30.8	14	99.0	45	167.2	76
33.0	15	101.2	46	169.4	77
35.2	16	103.4	47	171.6	78
37.4	17	105.6	48	173.8	79
39.6	18	107.8	49	176.0	80
41.8	19	110.0	50	178.2	81
44.0	20	112.2	51	180.4	82
46.2	21	114.4	52	182.6	83
48.4	22	116.6	53	184.8	84
50.6	23	118.8	54	187.0	85
52.8	24	121.0	55	189.2	86
55.0	25	123.2	56	191.4	87
57.2	26	125.4	57	193.6	88
59.4	27	127.6	58	195.8	89
61.6	28	129.8	59	198.0	90
63.8	29	132.0	60	200.2	91
66.0	30	134.2	61	202.4	92
68.2	31	136.4	62	204.6	93
70.4	32	138.6	63	206.8	94
72.6	33	140.8	64	209.0	95
74.8	34	143.0	65	211.2	96
77.0	35	145.2	66	213.4	97
79.2	36	147.4	67	215.6	98
81.4	37	149.6	68	217.8	99
				220.0	100

(Part III)

Diet per Kilo Body Weight in Health

Age	Gm carb	Gm prot	Gm fat	Calories
To 4 years	10.0	3.0	3.10	80
4 to 10 years	10.0	1.5	2.66	70
10 to 17 years	7.5	1.5	2.66	60
17 to 25 years	6.0	1.5	2.10	45
Adult	5.0	1.0	0.66	30

Use the table below, the one above is merely for comparison

Diabetic Diet per Kilo Body Weight

Age	Gm carb	Gm prot	Gm fat	Calories	Physical activity
To 4 years	6.0	3.0	2.0	50	
4 to 10 years	6.0	1.5	2.0	44	
10 to 17 years	4.0	1.5	2.0	40	Very active
17 to 25 years	3.6	1.0	2.0	36	Average
c Adult—Male	5.0	1.0	1.5	50	Light work
—Female	2.6	0.75	1.25	25	Indoors

TABLE 13.—CARBOHYDRATE, PROTEIN, AND FAT ALLOWANCES (BARACH)

Carbohydrate Portion

d

Carbohydrate	50	60	70	80	90	100	110	120	130	140	150	160	170	180	100	200	210	220	230	240	250
	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm
Food.																					
6 per cent fruit ..	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	135	200	235	300	305	400
Cereal (dry weight) .	14	20	25	28	31	25	28	34	37	24	31	40	28	31	37	40	40	40	40	40	40
Bread						20	20	20	20	40	40	40	00	00	00	00	00	00	00	00	00
20 per cent vegetable ..	50	50	60	70	00	00	70	00	110	120	140	150	170	100	100	170	100	200	170	100	200
6 per cent fruit.....	115	105	185	200	200	200	200	200	200	200	200	200	200	200	200	200	200	235	200	200	235
Bread.....						20	20	20	20	20	20	20	20	20	40	40	40	40	00	00	00
20 per cent vegetable	50	50	50	50	50	50	70	80	100	120	130	150	170	180	150	170	180	150	170	180	200
6 per cent vegetable	00	80	100	100	135	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
6 per cent fruit.....	60	85	130	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Bread.....			20	20	20	40	40	40	40
Grams protein incidentally obtained, and therefore to be subtracted from Protein-Fat Portion.....	...		5	5	5	5	0	10	10	10	10	10	10	10	15	15	15	15	20	20	20

Protein and Fat Portion

	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Protein																
Fat (incidental)	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Grams meat	25	30	40	50	60	70	85	90	100	105	115	125	135	140	150	160
Breakfast																
Lunch	25	35	40	50	60	70	75	85	90	100	110	115	125	135	140	150
Dinner	25	35	45	50	60	70	75	85	95	100	110	120	125	135	145	160

Additional Fat Portion

	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85
Additional fat.																
Butter	4	8	7	10	12	12	15	17	19	21	23	22	22	22	22	22
Fat salad or olive oil																
Butter or mayonnaise	4	6	8	10	12	14	15	17	19	21	23	22	22	22	22	22
Fat, salad or olive oil												3	2	8	12	14
Butter or mayonnaise	4	6	8	10	12	15	17	10	21	23	25	24	24	24	24	24
Fat, salad or olive oil											3	5	10	10	11	18

TABLE 15.—PERCENTAGE VEGETABLES AND FRUITS

3 per cent (sometimes called 3 per cent)

Vegetables (fresh)

Artichokes (French, as used for salad)
 Asparagus
 Beans, green or wax (or canned)
 Beet greens
 Broccoli
 Brussels sprouts
 Cabbage
 Cauliflower

Celery
 Cucumbers
 Egg plant
 Endive
 Green peppers
 Leeks
 Lettuce
 Marrow
 Mustard greens
 Okra
 Pickles (sour)
 Radishes
 Rhubarb
 Sorrel
 Sauerkraut (or canned)
 Spinach

Summer squash
 Swiss chard
 Tomatoes
 Watercress

6 per cent (sometimes called 10 per cent)

Vegetables

Beets
 Carrots
 Dandelion greens
 Kale
 Kohlrabi
 Onions

Oyster plant
 Pumpkin
 Rutabaga
 String beans
 Squash
 Turnips

Avocado
 Blackberries
 Cranberries
 Gooseberries
 Grapefruit
 Lemons
 Limes

Fruits
 Muskmelons, cantaloupe, honey dew
 Oranges
 Peaches
 Pineapples
 Strawberries
 Tangerines
 Watermelon

15 per cent

Vegetables

Artichokes (Jerusalem, or "ground," fresh, when cut into chips and dried, reckon the G value per Gm doubled)

Green peas
 Lima beans (canned)
 Parsnips
 Salsify
 Yams

Apples
 Apricots
 Blueberries
 Cherries
 Currants
 Grapes
 Guavas

Fruits

Huckleberries
 Nectarines
 Papaws
 Pears
 Plums
 Quinces
 Raspberries

20 per cent or higher

Vegetables

Baked beans
 Shelled beans
 Green corn

Potatoes (baked or boiled)
 White
 Sweet

Fruits
 Bananas
 Figs (fresh)
 Prunes

TABLE 16—MEAT EXCHANGES (BARACH)

Instruction—If your patient will eat to broil about among the meats, or to substitute fish, chicken, or eggs for some of the meat allowance, this can be easily arranged for him. For example, suppose a patient has been told in Table 14, a 100 Gm. meat for dinner. Let him have broiled turkey in the form of 70 Gm. chicken or turkey plus 30 Gm. butter, as shown in the Table (probably the 100 Gm. allowance). But that, like a clap net, he would prefer turkey, he would need then only have him omit the 70 Gm. of chicken or turkey, and the 8 Gm. butter which go with it, and take on 60 Gm. American chicken, dropping at the same time another 8 Gm. of butter.

(Cooked Meats)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
GRAMS OF MEAT																										
LEG OF LAMB plus Butter	25 -2	30 +3	35 +4	40 +5	45 +6	50 +7	55 +8	60 +9	65 +10	70 +11	75 +12	80 +13	85 +14	90 +15	95 +16	100 +17	105 +18	110 +19	115 +20	120 +21	125 +22	130 +23	135 +24	140 +25	145 +26	150 +27
ROUND STEAK plus Butter	18 -4	21 +5	25 +6	28 +7	32 +8	36 +9	40 +10	44 +11	48 +12	52 +13	56 +14	60 +15	64 +16	68 +17	72 +18	76 +19	80 +20	84 +21	88 +22	92 +23	96 +24	100 +25	104 +26	108 +27	112 +28	116 +29
SIRLOIN STEAK plus Butter	20 -4	25 +5	30 +6	35 +7	40 +8	45 +9	50 +10	55 +11	60 +12	65 +13	70 +14	75 +15	80 +16	85 +17	90 +18	95 +19	100 +20	105 +21	110 +22	115 +23	120 +24	125 +25	130 +26	135 +27	140 +28	145 +29
CHICKEN OR TURKEY plus Butter	16 -2	20 +3	24 +4	28 +5	32 +6	36 +7	40 +8	44 +9	48 +10	52 +11	56 +12	60 +13	64 +14	68 +15	72 +16	76 +17	80 +18	84 +19	88 +20	92 +21	96 +22	100 +23	104 +24	108 +25	112 +26	116 +27
ORIO BEEF plus Butter	16 -4	20 +5	24 +6	28 +7	32 +8	36 +9	40 +10	44 +11	48 +12	52 +13	56 +14	60 +15	64 +16	68 +17	72 +18	76 +19	80 +20	84 +21	88 +22	92 +23	96 +24	100 +25	104 +26	108 +27	112 +28	116 +29
CORNEO BEEF plus Butter	10 -1	12 +2	14 +3	16 +4	18 +5	20 +6	22 +7	24 +8	26 +9	28 +10	30 +11	32 +12	34 +13	36 +14	38 +15	40 +16	42 +17	44 +18	46 +19	48 +20	50 +21	52 +22	54 +23	56 +24	58 +25	60 +26
LAMB CHOPS, ROAST BEEF minus Butter	22 -2	26 +3	30 +4	34 +5	38 +6	42 +7	46 +8	50 +9	54 +10	58 +11	62 +12	66 +13	70 +14	74 +15	78 +16	82 +17	86 +18	90 +19	94 +20	98 +21	102 +22	106 +23	110 +24	114 +25	118 +26	122 +27
LIVER (weigh raw) plus Butter	25 -5	30 +6	35 +7	40 +8	45 +9	50 +10	55 +11	60 +12	65 +13	70 +14	75 +15	80 +16	85 +17	90 +18	95 +19	100 +20	105 +21	110 +22	115 +23	120 +24	125 +25	130 +26	135 +27	140 +28	145 +29	150 +30
TONGUE (pickled) minus Butter	38 -3	46 +4	54 +5	62 +6	70 +7	78 +8	86 +9	94 +10	102 +11	110 +12	118 +13	126 +14	134 +15	142 +16	150 +17	158 +18	166 +19	174 +20	182 +21	190 +22	198 +23	206 +24	214 +25	222 +26	230 +27	238 +28
FRIED HAM minus Butter	22 -2	26 +3	30 +4	34 +5	38 +6	42 +7	46 +8	50 +9	54 +10	58 +11	62 +12	66 +13	70 +14	74 +15	78 +16	82 +17	86 +18	90 +19	94 +20	98 +21	102 +22	106 +23	110 +24	114 +25	118 +26	122 +27
FRESH HAM STEAK minus Butter	15 -2	18 +3	21 +4	24 +5	27 +6	30 +7	33 +8	36 +9	39 +10	42 +11	45 +12	48 +13	51 +14	54 +15	57 +16	60 +17	63 +18	66 +19	69 +20	72 +21	75 +22	78 +23	81 +24	84 +25	87 +26	90 +27
SPARE RIBS minus Butter	20 -3	24 +4	28 +5	32 +6	36 +7	40 +8	44 +9	48 +10	52 +11	56 +12	60 +13	64 +14	68 +15	72 +16	76 +17	80 +18	84 +19	88 +20	92 +21	96 +22	100 +23	104 +24	108 +25	112 +26	116 +27	120 +28

FRIED HAM minus Butter and Eggs					8	14	18	23	28	32	36	40	45	50	27	32	36	40	45	60	55	60	64	88	72	76	82
					-1	-2	-4	-4	-4	-4	-5	-5	-6	-7	-4	-5	-5	-5	-6	-8	-8	-9	-9	-10	-10	-11	-11
					1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
BACON (Lean) weigh raw • minus Butter	34	40	47	54	60	67	73	80	87	94	102	107	113	120	127	134	140	146	153	160	167	174	180	188	195	201	
	-10	-12	-14	-16	-18	-20	-22	-24	-26	-28	-30	-32	-34	-36	-38	-40	-42	-44	-46	-48	-50	-52	-54	-56	-58	-60	
TUNA FISH, SARDINES (canned) plus Butter	21	26	30	34	39	43	47	51	55	59	63	68	72	76	80	84	89	93	98	102	106	110	114	118	122	126	
	+1	+1	+1	+1	+1	+2	+2	+2	+2	+2	+2	+3	+3	+3	+3	+4	+4	+4	+4	+4	+5	+5	+5	+5	+5	+6	
SALMON (canned) plus Butter	22	26	30	35	40	45	50	55	60	64	68	72	76	80	85	90	95	100	104	109	114	118	122	127	131	136	
	+2	+2	+3	+3	+4	+5	+5	+5	+6	+6	+7	+7	+7	+8	+9	+10	+10	+11	+10	+11	+12	+13	+13	+14	+14	+16	
SPANISH MACKEREL plus Butter	20	25	29	33	37	42	46	50	54	58	62	66	70	74	78	83	88	92	96	100	104	108	112	116	120	124	
	+4	+4	+5	+6	+7	+8	+9	+9	+10	+11	+12	+12	+13	+14	+15	+16	+16	+17	+18	+19	+20	+20	+21	+22	+23	+24	
BLUE FISH plus Butter	18	22	26	30	34	38	42	46	50	54	58	62	66	70	74	78	83	88	92	96	100	104	108	112	116	120	
	+5	+5	+6	+7	+8	+9	+9	+10	+11	+12	+13	+14	+15	+16	+17	+18	+19	+20	+21	+22	+23	+24	+25	+26	+27	+27	
SALT COO plus Butter	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	118	120	
	+7	+8	+9	+10	+11	+12	+14	+15	+16	+17	+18	+20	+21	+22	+23	+24	+26	+27	+28	+29	+30	+32	+33	+34	+35	+36	
SHAO, WHITE FISH, HALIBUT, LAKE TROUT plus Butter	Approx. Values	24	28	31	35	38	42	45	48	52	56	60	64	68	72	76	79	82	86	90	94	97	101	105			
		+2	+3	+3	+4	+4	+4	+4	+4	+5	+5	+5	+6	+6	+7	+8	+8	+9	+9	+10	+10	+11	+11	+12	+12	+12	
AMERICAN CHEESE minus Butter	16	19	24	27	30	34	37	40	44	48	52	55	58	62	66	69	73	75	79	83	86	90	93	97	100	104	
	-1	-1	-2	-2	-3	-3	-3	-4	-4	-4	-4	-4	-5	-5	-6	-6	-7	-7	-7	-7	-8	-8	-8	-9	-9	-9	
COTTAGE CHEESE plus Butter	24	30	36	40	44	48	52	57	62	66	71	76	81	86	91	96	100	105	109	114	119	124	128	132	137	142	
	+6	+8	+9	+10	+11	+12	+14	+15	+16	+17	+18	+20	+21	+22	+23	+24	+26	+27	+28	+29	+30	+32	+33	+34	+35	+36	
EGGS	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	4	4	4	4	4	4	5	5	5	

Hams to be broiled until crisp—placed on paper to absorb fat.

TABLE 17—SUPPLEMENTARY INFORMATION ON FOODS

Diabetic Foods—Most of the commercial "diabetic foods" are very low in carbohydrate but many of them are also high in protein. It is best to forbid their use.

Saccharin.—Benzosulfimide (saccharin) is an antiseptic and tends to hinder slightly the action of the digestive ferments an excessive quantity of it may, therefore, impair digestion. More than 5 grains (0.32 Gm.) per day has been pronounced harmful by the Government Referee Board of Chemists. In the moderate doses in which it is used for sweetening beverages of diabetics it is not likely to do harm. Cooking makes it somewhat bitter, add it late. As a flavored vehicle in which medicines may be administered to the diabetic, the following serves, being similar in taste to aromatic elixir.

Compound spirit of orange	xxx	0 60
Gluside (saccharin)	gr 3	0 06
Alcohol	5j	30 00
Water to make	5 v	120 00

Glycerin.—This substance may also be used in sweetening the food of diabetics in alternation with saccharin.

Seasoning.—Any of the ordinary seasoning agents may be used without reckoning them as food except that tomato catsup must be employed sparingly.

Jerusalem Artichoke.—The hubbly of this tuber's superiority seems to have been pricked by the studies of Soskin *et al* (1931), Stein *et al* (1931), and Campbell (1934), reckon it as any other 15 per cent vegetable.

Beverages.—Alcohol supplies energy to the body without yielding dextrose or fatty acids but diabetics away from home and alone should not drink any alcoholic beverages lest an insulin reaction be mistaken for intoxication if there is "liquor on the breath." *Whiskey, gin, rum* 1 ounce (32 cc.) will yield about 112 calories and need not be reckoned as food in the diabetic sense but if it is desired to replace food with it, then this amount will permit the omission of 28 Gm carbohydrate or 12 Gm fat. *Brandy* often has sugar added to it and should not be used. *Cordials* such as anisette, benedictine, chartreuse, crème de menthe, curaçao, kummel, etc., are very high in sugar and are to be forbidden. *Beer* and *ale* may be reckoned as containing not quite so much alcohol in a glass of 8 ounces (240 cc.) as there is in 1 ounce of whiskey, they will therefore supply nearly as many calories which do not require insulin for their production. But a glass of either of them will contain about 12 Gm. of carbohydrate that must be taken into account. *Wines and cider* vary too much in their sugar content to be safe. *Ginger ale* reckon about 20 Gm. of carbohydrate to the 8-ounce (240 cc.) glass. *Grape juice* is quite variable but the greatest amount of carbohydrate that a small glass (4 ounces, 120 cc.) is likely to contain is 24 Gm. *Cocoa* 1 large cup (8 ounces milk, 2 level teaspoonfuls cocoa, 1 level teaspoonful sugar), about 34 Gm carbohydrate, 8 Gm protein and 10 Gm. fat. *Tea and coffee* without sugar and cream, no food value, with sugar and cream (1 large cup 2 teaspoonfuls cream, 1 level teaspoonful sugar) equivalent to 10 Gm carbohydrate and 2 Gm fat.

Oysters.—One-half dozen on shell 4 Gm. carbohydrate, 6 Gm protein, 1 Gm fat.

Canned Shrimp.—One hundred Gm. contain 25 Gm protein, 1 Gm fat.

Olives.—Five ripe olives (or 10 green ones), 1 Gm carbohydrate, 5 Gm fat.

Soup.—Bouillon or consommé skimmed of fat and strained, has no food value. This is true of most canned bouillons and bouillon cubes. Creamed soups are rich and variable and should not be used.

Macaroni (Cooked).—Reckon 1 cupful (200 Gm.) at 30 Gm carbohydrate, 6 Gm protein, 3 Gm fat.

Crackers.—Twenty Gm. of crackers (3 graham's, or 3 sodas, or 5 small saltines) may be reckoned at about 15 Gm carbohydrate, 2 Gm protein, 2 Gm fat.

Mushrooms.—Two hundred Gm. contain about 1 Gm fat, the protein and carbohydrate are largely unassimilable and need not be reckoned with.

Nuts.—The assimilable carbohydrate in 50 Gm. of almonds may be reckoned at only 2 Gm., but protein runs 10 Gm. and fat 20 Gm. Brazil nuts 3 Gm carbohydrate, 8 Gm protein, 33 Gm fat. Chestnuts, 20 Gm. carbohydrates, 3 Gm protein and 3 Gm fat. Peanuts, 3 Gm assimilable carbohydrate, 15 Gm. protein, 20 Gm fat. Pecans 7 Gm carbohydrate, 5 Gm protein, 35 Gm fat. English walnuts, 7 Gm carbohydrates, 8 Gm protein, 32 Gm fat, black walnuts, 5 Gm carbohydrate, 14 Gm protein, 28 Gm fat.

Gelatin.—Contains 85 per cent protein, practically no other food constituent. In sweetening bear in mind that each level teaspoonful of sugar yields 20 Gm carbohydrate.

TABLE 17 (Continued)

Ice Cream.—A portion (100 Gm.) of average commercial ice cream may be reckoned at 20 Gm. carbohydrate, 4 Gm. protein and 14 Gm. fat.

Milk.—A glass (240 cc.), 12 Gm. carbohydrate, 8 Gm. protein, 10 Gm. fat.

Butter and Oleomargarine.—Ten Gm. (a restaurant "square"), 8.5 Gm. fat; therefore the purist will frown just a little at an equal exchange of 1 Gm. butter or margarine for 1 Gm. oil or fat (see below).

Oils and Fats.—Lard, fat, Crisco, olive and salad oils are fat, Gm. for Gm. (see Butter, above).

Eggs.—Reckon 1 egg of average size at 6 Gm. protein and 6 Gm. fat.

Sugar.—Sugar is carbohydrate, Gm. for Gm.

Bread.—The differences between white, rye, and whole wheat are too slight to be of importance; 1 ordinary slice ($\frac{3}{4}$ inch, 30 Gm.), 16 Gm. carbohydrate, 3 Gm. protein.

HYPERINSULINISM AND IDIOPATHIC FUNCTIONAL HYPOGLYCEMIA

The well-known reaction to the injection of an overdose of insulin in the treatment of diabetes is due to the induction by this exogenous method of a temporary state of hypoglycemia; in recent years we have come to recognize a similar condition due to endogenous factors. That is to say, there are individuals, nondiabetic, who develop a state of hypoglycemia with all the attendant symptoms of insulin shock as described in *Diabetes*. Seale Harris, of Birmingham, Alabama, who first presented the entity in 1924, called it "hyperinsulinism," describing at the same time a state of "dysinsulinism" in which the condition of hypoglycemia was at times succeeded by a temporary one of hyperglycemia; a relatively large number of cases has since been reported. The epileptoid character of the convulsions in some of the severe cases has also given rise to the opinion that perhaps a number of individuals convicted of idiopathic epilepsy may be in reality sufferers from this newly recognized metabolic dyscrasia, but the studies of Ziskind *et al.* (1936) cause one to doubt that the relationship is a very frequent one. Cameron (1930) pointed out the ease with which night terrors in children are sometimes relieved by the administration of sugar; bizarre fatigue states in youngsters might also be hypoglycemic reactions, since comparable states of aggravating restlessness, obstinacy and silliness have been noted at times in adults preceding the onset of unconsciousness; indeed, Harris (1936) and others are showing that hyperinsulinism may simulate or be the underlying cause of many of the syndromes classified as neuroses or psychoses; Weinstein and Mattikow (1939), furthermore, have reported 2 cases in which angina pectoris was the predominating symptom. Attacks frequently appear when the blood sugar level has reached 70 mg. per cent, but not invariably; sometimes a patient will be in a serious state at 50 mg., while at another time he will have only mild symptoms or none at all at the same level. In fact, Hart and Liss (1940), in recent confirmation of other observers, find that in individuals not affected with this malady routine fasting blood sugar levels frequently fall below 80 mg.; that values under 70 without shock symptoms are common; and that there may be times when the blood sugar reaches as low as 28 mg.

without a reaction. Obviously then, it is only a low blood sugar accompanied by symptoms that will make the presumptive diagnosis possible.

It now begins to appear that the study of this disease is facilitated by considering each case as either one of organic hyperinsulinism, hypoglycemia secondary to hepatic disease, or functional hypoglycemia—at least Conn (1940), who has studied the matter for a number of years, considers that 80 to 90 per cent of the cases will fall into these three categories. It would therefore seem advisable to orient the therapeutic consideration toward this classification.

THERAPY

Organic Hyperinsulinism—Barring the very rare instances in which the syndrome is associated with hypofunction of the anterior pituitary gland or the adrenal cortices, the term "organic" applies here to an abnormality of the pancreas *i.e.*, an adenoma, a carcinoma, or generalized hypertrophy and hyperplasia of the islands of Langerhans. Of course the remedy is surgical. Conn's indications for exploration of the pancreas are (a) absence of extra pancreatic causes of hypoglycemia, (b) abnormally low level of blood sugar during symptoms and rapid relief by administration of dextrose, (c) repeated fasting blood sugar levels below 50 mg per cent when the patient has been eating an adequate diet, (d) depression of the fasting blood sugar level below 40 mg per cent by carbohydrate restriction. The value of the glucose tolerance test as an aid to diagnosis is a quite controversial question. Latterly, there has been a swing in favor of the insulin tolerance test (Fraser *et al.*, 1938, Burtness *et al.*, 1941) in which 5 units of regular insulin are given intravenously after twelve hours of fasting; it is said that two hours later there is no tendency for the blood sugar level to reach normal if an adenoma of the islets is present. John (1935) has used another sort of insulin test as a differential aid (see below under Functional Hypoglycemia). Complete cure has often resulted from the removal of an adenoma but several operations are often necessary to find the new growth or to locate and remove all the new growths—witness the case of Ziskind *et al.* (1937) in which autopsy revealed an adenoma which had not been found at two previous pancreatic resections. Sometimes simply partial or subtotal pancreatectomy is resorted to but the results are often disappointing. Conn points to the likelihood that in the successful cases very small, perhaps only microscopic, tumors have been removed.

Patients who refuse operation can only be treated as cases of functional hypoglycemia, without much prospect of success.

Hypoglycemia in Hepatic Disease—To rule out the possibility of an impairment of the glycogenic function of the liver acting in the causative role, it seems advisable to employ all the available tests of liver function. It is the contention of Coller and Jackson (1939), and of Conn (1940), of the same group at the University of Michigan, that the glycogenic liver function may be disturbed by gallbladder disease and, therefore, that in certain instances of hypoglycemia cholecystectomy may be called for. Conn's indications are (a) postabsorptive hypoglycemia markedly intensified by dietary carbohydrate restriction, (b) postprandial hyperglycemia with intermittent glycosuria, (c) hyperglycemic plateau type of dextrose tolerance curve with abnormally low fasting level, (d) evidence of impaired function by other tests, (e) evidence of a diseased gallbladder by cholecystography, (f) presumptive

elimination of other causes of chronic degenerative and destructive lesions of the liver

Patients in this category who refuse operation can only be treated as a functional hypoglycemia Rector and Jennings (1937), reporting 11 cases of hypoglycemia with recurrent convulsions in infants and young children and reviewing previous reports, feel that in this group hypoglycemia is usually a functional hepatic disorder of intermittent character, resulting from temporary depletion of glycogen reserve

Functional Hypoglycemia—A few of these cases, in which there are no evidences of hepatic, pancreatic or other organic involvement, are seen in pregnancy and lactation in individuals who are at severe continuous muscular work, or in cases of very severe renal glycosuria, but in most instances the good old term "idiopathic" must still be applied These are, however, the cases which usually respond to dietary treatment, occasionally drugs are also helpful

Dietetics—In cases of mild severity the taking of a little food that is high in quickly assimilable carbohydrate, between meals and late at night is usually sufficient to control the symptoms, the frequent drinking of sweetened orange juice or lemonade and the munching of candy is successfully resorted to by many individuals who have recognized the necessity of frequent feeding in their own cases In going over collected case reports one not infrequently encounters the statement that the patient has for a long time been setting his clock to awaken him in the early morning hours for the snack of food which will prevent his lying helpless in bed at the time when he should arise for the day These facts being recognized, not unnaturally in the beginning of the study of this disease patients were put on high carbohydrate diets, but soon it was realized that these diets very frequently resulted in an increased number of attacks, the large amounts of carbohydrate ingested affording an added stimulus to insulinogenesis with a resultant quick slide into hypoglycemia

The first definite advance in the dietetic treatment consisted in the use of a diet low in carbohydrate, high in fats, normal or slightly below normal in proteins, and frequent feedings Harris, the originator of this regimen, believes that there is advantage in using the low percentage fruits and vegetables since their slow digestion yields only small quantities of glucose at a time, by which he believes that the minimum stimulation of insulin secretion is accomplished Fats, particularly in the form of cream and milk, given with and between meals are believed to delay assimilation of carbohydrate by inducing slow emptying of the stomach The diet in each case must of course meet the patient's nutritional requirements For adults of average height and weight, Harris allows about 2250 calories, 90 to 150 Gm of carbohydrate, 60 to 75 Gm of protein and the rest fats, largely cream and butter, this being divided among five to seven daily feedings (The reader will find dietetic tables under Diabetes) Obesity is a not infrequent accompaniment of hyperinsulinism In such cases, Harris uses 120 Gm of carbohydrate, 60 Gm of protein and only 60 Gm of fats (1260 calories), with six to eight feedings daily Activities are restricted and the carbohydrate increased to 150 to 200 Gm, or even more if the patient becomes weak or is losing more than 2 pounds (900 Gm) weight per week Underweight, asthenic patients are allowed 90 to 150 Gm carbohydrate, 200 to 300 Gm fats and 60 to 75 Gm protein, with five or six feedings a day

The next advance consisted in the substitution of a high protein for a high fat diet by Conn, who justifies his diet upon the following basis (a) Protein is absorbed slowly (b) Protein yields about 58 per cent of itself as carbohydrate but it does so very slowly and there results no hyperglycemia and consequently no resultant hypoglycemia Conn's recommended diet contains 120 to 140 Gm of protein, 50 to 75 Gm of carbohydrates, and the remainder fats in order to make up the necessary calories for maintenance, he says that Wilder has also had good results at the Mayo Clinic, using about 2 Gm of protein per kilogram body weight

Drugs—*Epinephrine* (adrenalin), in the usual dose of 0.5 to 1 cc of the 1:1000 solution, is used to rouse the patient from a severe attack Conn (1940) finds that supplementing the high protein dietary régime with subcutaneous injections of small amounts of the drug twice daily sometimes satisfactorily kept the blood sugar above the attack level and did so without increasing the oxidation of carbohydrate He thinks it likely that "slow epinephrine" (see Asthma) might be a valuable adjunct to therapy in some cases *Ephedrine* has been used only with doubtful results so far *Pituitrin*, in injections of 0.5 to 1 cc, is sometimes effective in emergencies, as is also *caffeine* in the form of caffeine sodiobenzoate, 5 grains (0.3 Gm) or more, Harris says that a cup of coffee or a glass of coca-cola is so effective as to serve in some instances as a diagnostic test Allan proposed the use of *thyroid substance* as in myxedema, but after several years' trial he stated in 1935, that he felt it did not give substantial results John (1935) felt that in functional cases if *insulin* is given hypodermically after meals before the post prandial blood sugar rise stimulates the production of insulin, the amount of endogenous insulin will remain low enough to prevent hypoglycemic symptoms He gave 10 to 20 units of insulin after meals and was highly pleased with the results Harris finds *phenobarbital* helpful in doses of 1½ grains (0.1 Gm) night and morning in cases difficult to control or in patients who will not adhere to the diet, *bromides* are also effective, it seems, but he counsels against their employment because of bromism Occasionally he has obtained good results with *belladonna*, however, Quigley (1937) warns against the use of atropine

To bring a patient out of an attack when he cannot cooperate to the extent of swallowing sugar or orange juice, the intravenous injection of *dextrose* must be resorted to 10 Gm in 50 to 100 cc of sterile physiologic salt solution or, as preferred by some men, a smaller amount of a more concentrated solution

DIABETES INSIPIDUS

Diabetes insipidus is a disease characterized by the excretion of quite enormous amounts of urine and a resultant loss of tissue fluids which has to be compensated by the ingestion of equal quantities of water The urine is practically colorless, does not contain sugar, is of very low specific gravity, and contains none of the elements suggestive of renal involvement There is no decrease in the flow of saliva the mucus becomes thick and tenacious

there is constipation, practically no sweating, and the skin becomes very harsh and dry. The patients are made very miserable by the necessity to urinate so often and to be constantly drinking water. This excessive water drinking usually causes the appetite to become abnormal because of the necessity for a great number of calories in order to bring all the water to body temperature, if, as is often the case, only cold water will be taken, there is in addition shivering 'gooseflesh,' weakness and tremor. The disease may occur at any age but is most frequent in young adults, in recent years a great many cases have been described. The onset is usually gradual though in some cases it has been quite sudden.

Cranial injuries, brain tumors, encephalitis and other diseases of the central nervous system (especially syphilis), abdominal aneurysm, tuberculous peritonitis, and other disturbances have been associated with diabetes insipidus a number of times, but in many cases it is not possible to trace a connection of this sort. It would seem that in this disease the pituitary body is at fault through failure to supply a necessary hormone from its posterior portion, but at present we have little more precise information than this fact. There is now conclusive evidence that the disease also exists in an hereditary form which is compatible with the normal length of life in those surviving infancy.

Diabetes insipidus was described by Johann Peter Frank, in 1794. Cushing and his coworkers first drew attention to the apparent hypophyseal relationship in 1912.

THERAPY

Pituitrin—In the vast majority of cases hypodermic injections of pituitrin control the symptoms of this disease, that is to say, the polyuria ceases or is very markedly reduced and there is then a corresponding decrease in the craving for water. The dose necessary to accomplish relief is usually 1 cc of the obstetrical pituitrin, or of pitressin, but the duration of the relief varies from four to forty-eight hours, in 16 of a series of 26 cases reported by Rowntree, it was twenty-four hours at least. Most patients prefer to take the injection at night in order to have their greatest period of freedom during the sleeping hours, for the necessity to be urinating frequently throughout the night is one of the most distressing features of the disease. Since peristalsis is sometimes markedly increased by pituitrin, it is advisable to have the injection taken about two hours before bedtime in order to permit a visit to the stool before retiring. The continued use of the drug over a long period of time gives rise to no serious untoward effects, however, it may be wise to counsel cessation of water ingestion very soon after taking the injection, for with a sudden decrease in water elimination there is some danger of water 'intoxication' if fluid continues to be poured into the system.

Blumgart reported a series of cases in which intranasal application of the pituitrin was fully as satisfactory as subcutaneous injection. From 0.5 to 5 cc of obstetrical pituitrin was sprayed into the nose every three to four hours, or a cotton plug soaked in 1 cc was introduced high up into the nasopharynx of one nostril at a time at intervals of four or more hours. Rowntree also states that he has had good results with this method. Vidgoff (1932) obtained satisfactory results with freshly desiccated powdered posterior pituitary tissue applied to the nasal mucosa by means of the fingertip. Extract incorporated in jelly was found to be less effective and more expensive. Smith (1934) has 40 to 50 mg of the powder blown up into the nose from a powder

blower, Marble (1935) uses this method also, it being much cheaper than any of the others, but one of his patients successfully took the powder in the old fashioned method of taking snuff, as has Canelo and Lissers (1935) patient also. Greene and January (1940) have reported 5 cases in which they used subcutaneous injections of a suspension of pitressin tannate in oil, the duration of the drug's activity was considerably prolonged in all cases thus necessitating fewer injections.

In 1932, Zondek and his associates in Germany described a new substance—intermedin—derived from the pars intermedia of the pituitary body. Sulzberger (1933) used the preparation obtained from Zondek successfully in 2 cases, in the United States and Turner (1935), using a preparation made for him by Parke Davis, was successful in his 5 cases though response was not so great as with pituitrin. Dischreit (1935), in Germany, apparently failed completely.

Miscellaneous Measures—Scherf (1932) reported 5 cases treated with large doses (30 grains 2 Gm., daily for five days) of amidopyrine (pyramidon), in 4 of which marked diminution in symptoms was induced. The effect was of only short duration but could be obtained again after a short interruption of the treatment, the effectiveness of pituitrin was not altered by changing for a while to amidopyrine. De Gown (1935), confirmed the efficacy of this drug however, because of its tendency to cause agranulocytosis, it should be used only under hematologic control.

Treatment of associated diseases, such as syphilis is of course indicated and will nearly always result in an improvement in the general health, such measures alone rarely bring about any reduction in the polyuria however. Surgical removal of associated tumors has sometimes corrected the condition. Rowntree says "Spinal puncture is a desirable procedure in all cases unless contraindicated by the presence of an intracranial neoplasm" though it is not apparent in the record that it was worth much in his series of cases. Cures have followed upon this procedure but it is well to bear in mind that spontaneous cure is not unknown in this unique disease.

It is usually the practice to reduce the patient's intake of sodium chloride to the practically irreducible minimum, a measure which in itself is often very helpful.

Blotner and Cutler (1941) performed total thyroidectomy in 3 cases, in 2 cases which were of postencephalitic origin, the results were satisfactory but in 1 case, which was idiopathic in nature, there was no effect, though the authors felt this failure was likely due to the presence elsewhere of accessory thyroid tissue. In Findlay's (1937) case, ablation of the thyroid was no more effective in reducing urine output than a low salt diet but it did increase the patient's responsiveness to pitressin and diminish his diuretic response to sodium chloride.

Weinstein and Spingarn (1940) report a case following, and presumably incited by, a middle ear infection, which terminated after deep roentgen therapy to the pituitary region.

DISTURBANCES IN MENSTRUATION

DISTURBANCES IN MENSTRUATION

SEX HORMONE THERAPY IN MENSTRUAL DISTURBANCES

There is nothing more fascinating to me in the whole of medical literature than the pretty pictures, especially those in colors, showing how the various anterior pituitary and ovarian hormones may be assumed to regulate the menstrual cycle. But there is no proof in that same literature, nor even any strongly suggestive evidence based upon controlled clinical experimentation, that such regulation can be effected at will by the administration of commercially available preparations of the allegedly specific hormones. Much knowledge of menstrual and reproductive physiology has been gained, and we may confidently look forward to the time when all, or nearly all, the mysteries will have been solved, for many men of excellent training, high intelligence and unimpeachable integrity are at work in these fields—but as yet the only reasonably reliable measure available for practical use by the general practitioner is estrogen therapy for symptomatic relief in the menopause (which is duly described in the proper section below). The Council on Pharmacy and Chemistry of the American Medical Association accepts and describes in *New and Non Official Remedies* (1941) only the naturally occurring estrogenic substances for use in the menopause exclusively. I must still advise the reader, as was done in the preceding edition of the book four years ago, to spend his memorizing ability upon something other than the names of the sex hormone products of the competing pharmaceutical houses.

AMENORRHEA, HYPOMENORRHEA, OLIGOMENORRHEA AND DELAYED MENSTRUATION

The first of these terms means absence of menstruation, the second scanty menstruation, the third infrequent menstruation and the fourth what the term implies. Other than menopause, of which amenorrhea is one of the signs, its most frequent cause is of course pregnancy and the height of lactation. Other very simple things may bring about these disturbances, especially in girls and younger women, such as change in climate or environment, exciting or frightening emotional experiences, a love affair, etc. More serious causes are the acute infectious diseases, or such chronic affections as tuberculosis, diabetes mellitus, the deficiency and hematologic disturbances. In several psychoneurotic maladies, especially anorexia nervosa, these disturbances in menstruation may present, and they occur at times in hypothyroidism and regularly as one of the presenting signs of several of the classical endocrinopathies. That some cases, otherwise unexplainable, are due to ovarian and anterior pituitary hormonal imbalances is nowadays accepted teaching but the true hormonal regulation of bleeding

has not yet been completely elucidated. Of course pelvic tumors, malformations or inflammatory disturbances can appear in the causative role.

THERAPY

The occurrence of one of these menstrual irregularities which is not patently due to a transiently disturbing element in the patient's life should be accepted as a signal for a thorough study directed toward the unearthing of one of the underlying maladies listed above. The treatment then becomes the treatment of the primary disturbance. Otherwise, that is to say if all examinations reveal a completely healthy woman who simply is not menstruating often enough or sufficiently to satisfy her or her mother or grandmother, one thing that can be done apparently with considerable hope of success is to administer thyroid substance as in hypothyroidism. Why it should be effective no one knows. In a series of 25 cases of delayed menstruation in women who had had a normal menstrual history up to the last period, Soskin *et al* (1940) succeeded in each instance in causing the flow to start in an average time of twenty-eight hours by the administration of prostigmine methylsulfate, with one exception all the patients reported normal menstruation at their next regular period. The dosage ranged from 1 to 3 intramuscular injections of 1 or 2 cc of the drug in 1:2000 solution. Soskin goes so far as to say that if a woman fails to menstruate after the use of this drug pregnancy may be diagnosed as accurately as with the Friedman test. Winter (1940) could not confirm this position since the test failed in one of his 4 cases, however, it succeeded in the 6 cases of Cherniack and Sheps (1941).

Actually, the mere absence of menstruation is in itself nothing to be greatly agitated about. Oftentimes the beginning of satisfactory sexual life establishes or reestablishes the flow, but many women have gone into marriage while amenorrheic and have become pregnant all the same.

MENORRHAGIA AND METRORRHAGIA

The first of these terms means prolonged or profuse flow, and the second flow at irregular intervals between the periods but they can probably be satisfactorily designated here by the single term excessive bleeding. Sometimes such bleeding occurs just as a girl reaches maturity and does not recur, but it may take place at any time during or even after, a woman's menstrual life. In most of the latter, postmenopausal instances the cause is a neoplastic growth, but the fact is not to be overlooked that such growths may occur and cause excessive bleeding in younger women also. Other conditions giving rise to bleeding which is usually slight and of the 'spotty' kind peculiar to older women, are senile endometritis and vaginitis. In younger women the causes are most frequently found among the following: tubal pregnancy, threatened abortion, retained gestational products, retrodisplacement, ovarian cyst, uterine fibroids or polyps, endometrial hyperplasia, pelvic inflammatory disease. Excessive bleeding may occur in either hypo- or hyperthyroidism and is seen in some of the other classical endocrinopathies. Likewise it prob-

ably occurs as a reflection of some of the less understood pituitary-ovarian imbalances. Coagulative heart failure, hypertension, leukemia, hemophilia, thrombocytopenic purpura, the acute infectious diseases—Danforth (1935) includes even syphilis—may be partially manifested in excessive bleeding.

THErapy

I think it obvious that therapy must be directed by diagnosis made through a process of exclusion, and that these matters, most of which are gynecologic, cannot be presented in this book. Of course bleeding after the termination of the menstrual life always calls for manual and speculum examinations and sometimes diagnostic curettage as well. In young girls bleeding excessively for their first few periods, rest in bed, an ice bag to the lower abdomen, and ergot are time tried remedies. The latter is probably more successful since ergotamine tartrate (gynergen) has become available; it is usually injected intramuscularly in 1 cc dosage, repeated in an hour if necessary, and followed by a tablet orally three or four times daily for several days, one should remember that ergot is capable of causing severe poisoning. As in scant or no bleeding, so in these cases of excessive bleeding thyroid substance is often of value. Foster and Thornton (1939) relieved 12 of their 13 patients with metrorrhagia and 6 of their 7 with menorrhagia. It is rare for a patient who is not a youngster to escape successive dilatation-curettings. The men of my time in hospital were given to understand that a diagnostic curettage is one thing and a therapeutic one quite another, but attitudes seem to have changed radically in this matter, for nowadays many men who would not attempt other radical surgery seem to feel competent to perform this neat little operation. Of course I am not qualified to pass upon such things.

ESSENTIAL DYSMENORRHEA

(Painful Menstruation)

Perhaps more than 50 per cent of women suffer from dysmenorrhea, the symptoms varying from a mild physical and mental discomfort to severe attacks of pain that wrack the patient's back, head, legs, and lower abdomen for several days and leave her in a state of great fatigue during the early part of the intermenstrual period. Grant that dysmenorrhea is only a symptom and not a disease, and classify the various types on an alleged causative basis, the fact will remain that there is a constitutional something underlying all the cases, that is to say, that the dysmenorrheic woman differs in some essential way from the nondysmenorrheic. This position is of course challenged, and the attempt is made to find a neuralgic, ovarian, congestive, obstructive, inflammatory, mechanical, autonomic, endocrine, or allergic cause in all cases—which would be very fine were it not for the fact that the very same causes are found in many individuals who do not have dysmenorrhea. Therefore, in the present state of our knowledge, the term "essential dysmenorrhea" would seem to be permissible.

THERAPY

Surgical Measures—Various surgical measures from bilateral ovarian denervation or presacral sympathectomy to hysterectomy are employed, of which perhaps the soundest theoretically is dilatation of the cervix in the attempt to convert the nulliparous uterus into a condition similar to that of the parous uterus, it being noteworthy that women who have suffered from dysmenorrhea frequently no longer do so after they have borne a child. This dilatation, however, oftentimes gives only temporary relief, in which cases the use of pessaries is advised in the hope of prolonging the asymptomatic period—a practice that many physicians look upon as vicious. It is also claimed that if the internal os is severed in addition to the dilatation, the percentage of permanent cures is greatly increased. This may be true, but since most of these patients will not consent to operation (even were it advisable to urge it, which is questionable), the method is of relatively little use. Carbon dioxide insufflation of the fallopian tubes has been advocated, but not all of those who have employed it have found it effective.

I believe that all but a relatively few enthusiastic gynecologists have given up the routine suspension of retroverted uteri, a truly heinous anatomical abnormality that has at one time or another been held responsible for all of the ailments of the daughters of Eve.

Exercise—Miller, in 1934, seemed to have convinced himself by careful study that faulty posture has nothing to do with dysmenorrhea, but in 1940 he expressed the opinion, which is certainly shared by many, that much benefit is often to be derived from prescribed exercises, especially in young women. The system of simple exercises which Clow described in 1932, follows (Of course these exercises are to be prescribed only for women otherwise healthy.)

TABLE OF EXERCISES FOR HEALTHY DYSMENORRHEIC WOMEN

- 1 *Floor Polishing* Kneel on all fours. Swing right arm with elbow stiff through a semi circle, as if polishing the floor, reaching as far forward and as far back as possible. Repeat swing ten times with each arm.
- 2 (a) *Bending* Stand with feet apart. Stretch arms above head, bend forward and touch ground with knees straight. Return to first position. Repeat slowly eight times.
(b) *Twisting* Stand with feet apart. Stretch arms to side on level with shoulders. Twist trunk round until right arm points directly backward. Twist again until left arm points directly backward. Repeat vigorously ten times.
(c) *Swaying* Stand with feet apart. Stretch arms above head. Sway body and arms to right then left. Repeat slowly ten times.
- 3 *"Rowing"* Sit on floor with knees straight and feet pressed against wall. Lean forward and touch wall with knuckles, allowing knees to bend slightly. Repeat rhythmically twenty times.
- 4 *Right to Left and Left to Right*. Stand with feet apart. Swing right arm up as far as possible. Bend down bringing right arm over and touch left foot. Repeat six times. The same with the left arm and right foot.
- 5 *Floor Pathing* Kneel, a tugging back on heels. Twist body and tap floor with both hands four times on left side. Kneel upright. Twist body and repeat tapping on right side. Repeat eight times each side.
- 6 *Bean Picking* Throw 20 small objects, such as beans on the floor. Pick up one at a time and place on a shelf above the head using hands alternately. Do it as quickly as possible.

Hygiene—There is no reason why the patient should not have as usual except that the tub bath may be esthetically objectionable. The shower or

sponge bath is still available, however, and if taken quite hot is often very helpful

Intranasal Therapy—The question of the interrelationship between the nose and the female generative organs was first raised by Fliess, in 1897, and in the years immediately succeeding gave rise to a considerable controversy among German otolaryngologists and gynecologists. The "genital spots" in the nose are the tuberculum septi (prominences on the upper anterior part of the nasal septum on each side) and the anterior portion of the inferior turbinate on each side. It is claimed that at menstruation these areas swell, become sensitive, and bleed easily. It would seem that treatment of these areas deserves some consideration, for Crossen, in 1926, collected the reports of 81 cases treated by three physicians, with success in 63 cases or 77 per cent. The method probably is laughed at too much and tried too little.

Method—Apply 20 per cent solution of cocaine to the genital spots during the height of the pains, if they cease, the case is likely to respond favorably to the treatment, which aims at permanent ablation of these spots and is instituted between periods. This consists of the application of trichloroacetic acid to the spots four times at intervals of about five days, allowing time between treatments for the disappearance of the slough that forms. The applications are painful and may be preceded by cocaineization.

Sedatives, Analgesics, and Antispasmodics—It is the rare and fortunate case that responds to the sedatives alone, these drugs are discussed under *Insomnia*. Likewise, it is unusual for a patient with severe dysmenorrhea to obtain complete relief from analgesics, but many patients do have the worst edge taken off their pain by them. Those most frequently used are acetanilid, 3 grains (0.2 Gm), acetphenetidin, 5 grains (0.3 Gm), and acetylsalicylic acid, 5 grains (0.3 Gm), caffeine citrate, 2 grains (0.12 Gm), combined with either of these sometimes enhances its power, though of course it may cause sleeplessness in some individuals. The above drugs should be given every three to four hours, beginning the day before the attack is expected. Amidopyrine in 5 grain (0.3 Gm) dosage is probably better than any of them, but its tendency to cause agranulocytosis should cause it to be withheld in any case in which hematologic studies cannot be made—a drastic statement, but probably justified by the evidence.

Alcohol is the analgesic par excellence in dysmenorrhea, as many patients know without being so instructed by the physician. I believe that there are plenty of women capable of taking alcohol in small amounts and at long intervals as a medicine. That the gynecologist fears this type of therapy more than does the general practitioner is probably due to the fact that the gynecologist, like all other specialists, knows his patient too little to have a valid opinion of her stability.

Opium will of course relieve this pain, but its use is very dangerous because of the great likelihood of inducing the habit. There are some cases, however, in which respite can be obtained by no other agent. Codeine is preferable to morphine or dilaudid, the $\frac{1}{4}$ grain (0.03 Gm) dose twice a day, or the $\frac{1}{2}$ grain (0.015 Gm) dose at shorter intervals is less completely analgesic than the stronger drugs, but it is also less constipative, less nauseant, and less depressant to the general metabolism. The danger of codeine habituation is practically nil.

In 1911, Novak of Vienna, being struck by the fact that many women with increased irritability of the autonomic nervous system suffer with dysmenorrhea, began the treatment of the condition by the oral administration of atropine, Drenkhahn having been applying the drug directly in the cervical canal for a number of years. In the experience of most physicians who continue to use the drug—and nearly all do, for there is occasionally a strikingly good result—the colicky pains are much more relieved than are the backache, bearing down in the lower abdomen, lassitude, etc. Ordinarily, $\frac{1}{100}$ grain (0.0006 Gm) is given three times daily, beginning two days before expected onset and continuing until the second or third day of menstruation.

The following prescription combines a sedative, $\frac{1}{2}$ grain (0.03 Gm) of phenobarbital, a member of the belladonna group of antispasmodics, extract of hyoscyamus, $\frac{1}{4}$ grain (0.05 Gm), and an analgesic, acetanilid, 3 grains (0.2 Gm.); the patient should begin the use of these capsules one day before the onset of the period is expected.

R	Phenobarbital	.. gr. vi	0 4
	Extract of hyoscyamus	. gr. vi	0 4
	Acetanilid	. gr xxxvi	2 3
	Make 12 capsules		
	Label: 1 capsule every four hours Not to exceed 4 doses daily		

Davis (1941) writes that the following drugs are employed in mixture at the Chicago Lying-In Hospital: camphor monobromate, $\frac{1}{2}$ grain; atropine sulfate, $\frac{1}{100}$ grain, papaverine hydrochloride, $\frac{1}{2}$ grain; phenacetin, 3 grains; acetylsalicylic acid, 3 grains. One might write such a prescription as the following.

R	Camphor monobromate	gr vi	0 4
	Atropine sulfate	gr. 1/40	0 0015
	Papaverine hydrochloride	gr. iij	0 2
	Acetphenetidin (phenacetin)	gr xxxvi	2 3
	Acetylsalicylic acid (aspirin)	gr xxxvi	2 3
	Make 12 capsules		
	Label: 1 capsule every four hours Not to exceed 4 doses daily.		

Latterly, benzedrine sulfate has been enjoying some vogue. In the experience of Hundley *et al* (1939) relief was obtained by the administration of $\frac{1}{2}$ grain (10 mg) in 61 per cent of 186 cases, an additional 14 per cent being relieved by taking a second 10-mg. tablet. In Taylor's (1941) experience with 34 cases, 40 per cent obtained complete and 40 per cent moderate relief; the dosage used was 5 to 20 mg a day. In Larkin's (1941) study of 159 cases through a period of six months the drug proved beneficial in mild dysmenorrhea only. One should not overlook the fact that benzedrine may apparently become a drug of addiction; furthermore it causes insomnia in many individuals, occasionally also arrhythmias are induced or accentuated.

Miscellaneous Agents.—The newest agents to be employed, rather as shots are taken into the dark it seems to me, are insulin and calcium. Altschul (1936) described good relief obtained with insulin in 10 of 12 cases; Schrick (1939) in 8 of 10 patients (Schrick gave 5 units of regular insulin daily before lunch for three to five days before each menstrual period). Of Boynton and Hartley's (1934) 49 calcium-treated patients, 33 were said to have been greatly benefited. It will take much time and careful work to show that the

diversion and psychic effects of these remedies are not their only valuable properties

Thyroid substance, used as in hypothyroidism, is frequently helpful for example, in Foster and Thornton's (1939) 25 cases the drug effected complete relief in 17 and partial relief in 5, in Shute's (1940) series of 180 cases the drug was effective far more often than any other agent or measure, effecting "cure" in 58 cases. One should not be reckless in the use of thyroid substance however, because dysmenorrhea is not unknown in patients with a slight hyperthyroid tendency and there exists at least the theoretical possibility of exaggerating this state

PERIODIC INTERMENSTRUAL PAIN

Some women experience discomfort, malaise, and uni- or bilateral intermittent pelvic pain of colicky nature and variable degree precisely halfway between their menstrual periods. At the present time this syndrome is variously attributed to uterine contractions, peristalsis of the tube or tubes, ovulation, distention or rupture of an ovarian cyst. The whole operative gamut has been run in these cases, but it is difficult to see how any therapy other than the use of sedatives and analgesics if necessary, could be really justified in the present state of our knowledge

PREMENSTRUAL TENSION

Several years ago Frank used the term 'premenstrual tension' to describe a syndrome occurring in the premenstrual phase a week or so preceding the menstrual flow and terminating sharply with the appearance of that flow. The most usual symptoms are headache, emotional instability, irritability, abdominal distention, nausea and vomiting, increased sex desire, pruritus and swelling of the vulva. In some instances the symptoms are severe in degree and the psychic alterations in particular may pose serious problems for the family of the sufferer

THERAPY

It is probable that Greenhill and Freed (1941) have made a valuable contribution in approaching this malady as a disturbance in electrolyte and water balance. At any rate they effected definite relief in 34 of 40 patients treated with ammonium chloride to prevent the retention of sodium in the tissues. The drug was given in 15 gram (1 Gm) doses three times daily, starting ten to twelve days before the expected period, the patient was asked to refrain from using table salt or sodium bicarbonate preparations during the treatment.

THE MENOPAUSE

At the period in their lives when involution of the ovaries takes place, which occurs usually between the forty fifth and fiftieth years, women pass through the climacteric state, of which either sudden or gradual disappearance of menstruation is the invariable and most outstanding manifestation. In about 16 per cent of women, indeed, it is the only manifestation save for the atrophy of the breasts (often masked by deposition of fat), uterus and external genitalia, which occurs more or less gradually during several succeeding years and is often but not invariably accompanied by some diminution in sexual desire and a slight alteration toward masculinity, and obesity. In an additional 4 per cent of women the only other symptom noted is slight "flushing." But in the remaining 80 per cent one or more of the following are experienced in variable degree: hot flushes, characterized by sudden dilatation of the skin vessels sweating and a sensation of suffocation often succeeded by a feeling of cold, precordial pain palpitation, and high blood pressure, arthritic pains, paresthesias, tinnitus, vertigo headache, insomnia, emotional instability, mental clumsiness, hypochondriasis, and depression with suicidal tendency.

THERAPY

This is not a disease but rather a natural transition in her life which every woman must experience. As a matter of fact, as Novak (1940) points out there are not a few women to whom the climacteric comes as a sort of boon, women who are transformed from a thin scrawny state after years of child bearing and domestic worry into a plumper, serene type of matron, a sort of second flowering. To be sure, some are disturbed much more than others and really suffer severe physical discomfort and mental disquiet, but we in medicine have as yet no magic wands at whose waving these things are invariably caused to pass. In the vast majority of instances with a moderate amount of disturbance the sedatives remain the best drugs. Thyroid extract is of value in patients tending toward the hypothyroid state. Sympathetic and understanding treatment in her home is to be fostered for the patient by acquainting the family with the nature of the disturbances and the extent to which their helpfulness will be of real assistance to her. A hobby, or anything that will prevent introspection, is to be encouraged. Travel, if it can be afforded is sometimes desirable, but on the other hand it may be harmful to a woman who will worry over the conduct of her home while she is away. The fear of cancer should be dispelled, by repeated examinations if necessary. Under the head of "estrogen therapy" below, I have attempted to present what may be currently expected from this type of treatment.

Estrogen Therapy—In the use of this term I mean the employment in therapy of the estrogenic substances obtained from pregnant human or mare's urine, estrone, estriol and estradiol, and the new synthetic compound stilbestrol (or more properly, diethylstilbestrol). Estrone (theelin) is Council accepted and is available in ampule form for intramuscular injection in dosage of 0.2 to 1.0 mg. one or more times weekly. Council accepted also is a monocrySTALLINE preparation of estrone, which is available in solution in oil for hypodermic use and in capsules for oral use, this preparation is known as amaiotin. Estriol (theclol) is Council-accepted and is available in capsules for so-called pulvules or kapsels for oral administration in doses of 0.06 to

0.12 mg. one to four times daily, either alone or supplementary to parenteral therapy. At the time of writing no preparation of estradiol is Council-accepted, but this substance, too, is much used. Stilbestrol, which bids fair to replace all the other preparations because of its relative inexpensiveness, is available in ampules of 1 and 5 mg. per cc. but is principally given by mouth in plain or enteric-coated tablets which range in size from 0.25 to 5.0 mg. the effective dosage in most practices seems to be between 0.5 and 5.0 mg. (see below).

Choice of Preparation—It is the consensus that equivalent results can be obtained with all these preparations provided suitable dosage adjustment is made.

Indications—Of course those who are making a special study of sex hormone therapy in the menopause are justifiably using these preparations a great deal, but for the general practitioner the fact cannot be too often reiterated that even among the small minority of women whose symptoms at the climacteric are severe enough to compel them to consult a physician there is a large proportion who are not likely to profit by estrogen therapy. For example, of 100 women admitted to the Boston Dispensary endocrine clinic because of severe menopausal symptoms, Lawrence and Moulyn (1941) found a positive test for prolactin in the urine in only 18. In 81 per cent of this positive group the symptoms were preponderantly those of vasomotor instability, which was, to be sure, definitely benefited by estrogen therapy in 90 per cent of instances. However, in the other 52 patients, whose test for urine prolactin was negative, treatment with these preparations caused improvement in only 25 per cent, whereas simple psychotherapy or sedation brought relief in over 80 per cent. These observers doubtless express the feeling of many practitioners who have had experience in this matter when they conclude: "A predominance of vasomotor symptoms in a menopausal woman is suggestive of an overactive prolactin production, but treatment with estrogens should not be instituted until urinary assay proves that prolactin is being excreted." Sharr (1940), too, who has contributed so much to the subject, through the development of a vaginal smear test for objective evidence of response to treatment, also makes a point of the fact that patients differ markedly in their sensitiveness to estrogen therapy—in about one fourth of his patients symptomatic relief occurred with relatively little change in the vaginal smear, in about one half relief was experienced at intermediate levels of vaginal change, and with the remainder complete relief was not obtained until full replacement and a follicular smear were achieved. If psychoneurotic symptoms in a woman in the climacteric persist after the altered vaginal smear indicates complete estrogenic replacement, it becomes easier to accept these symptoms as arising from causes other than the menopause.

Dosage—The wide variations in response from patient to patient, above discussed, together with the fact that there is as yet no general agreement as to what amount of symptomatic relief should really be sought, make it at present impossible to state anything like a standardized dosage of these preparations. However, as regards stilbestrol, in representative studies the dosage has been as follows: (a) Sevringhaus (1940) obtained relief with less than 0.5 mg. daily in 1 of 17 patients, in only 3 was it necessary to exceed 5 mg. (b) Shorr (1940) reported effective dosage to be between 2 and 4 mg. in 42 patients. (c) Taylor and Thompson (1941) found the usual minimal effec-

tive dosage in 80 patients to be 2 mg though there was a range from 0.5 to 6.0 mg. In his 40 patients Schwittay (1941) obtained best results with 1 mg daily for the first month and after that 0.5 mg but in 8 cases 1 mg was needed only twice weekly and 1 patient reported satisfactory results with 0.1 mg daily.

Methods—I shall present here the regimen adopted in Shorr's clinic at the New York Hospital where control is based upon the vaginal smear rather than upon change in the subjective symptoms alone.

(a) After preliminary examinations to rule out organic or psychiatric involvement as nearly as possible the patient is placed on graded doses until the full follicular phase in the smear indicates that complete replacement has been accomplished. During the four to five weeks of this course the attempt is made to correlate smear and subjective changes in order to judge the level of dosage at which optimal effects occur and also to determine the type of subjective symptom which will be relieved by estrogen therapy in the particular patient.

(b) Treatment is then interrupted in order to determine through observation of the speed and intensity with which symptoms recur the probable ease or difficulty of the eventual readjustment. Another reason for this rest period is to avoid inducing bleeding from too prolonged uterine stimulation even so bleeding occasionally occurs.

(c) Treatment is resumed after two weeks if the return of symptoms warrants it the dosage and level of the smear which gives optimal relief being selected.

Shorr observes that in favorable cases each succeeding course finds relief achieved with progressively smaller doses until the need for further continuance of therapy ceases entirely but not all cases respond so favorably by any means. Some observers feel that doses should be just enough to keep the patient comfortable and that reduction should then be steady and systematic with a view to facilitating adjustment to the postmenopausal status. Shorr says he has for the most part failed in such attempts and therefore prefers his type of therapy especially as he feels that estrogenic therapy *per se* does not interfere with the eventual transition.

Results—The classical peripheral circulatory changes the hot flashes headache asthma and insomnia seem to be the symptoms favorably affected with greatest regularity. Sevringhaus (1941) points out however that there are often variations in the results from day to day in a given patient. Observers disagree regarding the effect upon hypertension. Shorr however finds that well stabilized hypertension is scarcely or not at all affected but that those associated with emotional instability tend to stabilize at lower levels under estrogen therapy. Apparently some slight increase in libido is hoped for more often than it is achieved. Hall is probably the leader among those who believe that estrogen therapy will often relieve the joint symptoms so often present in association with the menopause though Shorr seems to be upon the whole in agreement with him, admitting however that these arthralgias may persist very severely despite most intensive estrogen treatment. Dunn (1949) says the arthritic state is the last to be relieved. Cohen *et al* (1940) allege that the benefits are striking but "of a general systemic nature, whatever that may mean. It seems to me significant that leaders in the study of the arthritides *per se* such as Cecil (1939) and

Hench (1939), have been much disappointed in their results with this type of therapy. A number of observers, perhaps most notably Werner *et al* (1936), have reported favorable responses to estrogen therapy in cases of involutional melancholia but Ripley *et al* (1940), of Shorr's group, are much more pessimistic. Heaver (1940) feels that experience has conclusively demonstrated that the stimulation resulting from estrogenic therapy may seriously aggravate the psychosis, he would not have the estrogenic substances employed in even severely neurotic, to say nothing of mildly or profoundly psychotic, patients. The fact should never be overlooked that the menopause may be all that is needed to precipitate a psychotic reaction that has been for a long time latent. Indeed, it seems that one of the most discouraging things in this type of treatment is the fact that an apparently satisfactory adjustment all along the line may be completely upset by the advent of a new psychic strain.

Danger of Inducing Cancer—It has been demonstrated that under certain conditions in the experimental animal the administration of estrogenic substances is capable of inducing the appearance of carcinoma. Whether this is also true in women under treatment with these substances is of course a question of utmost importance. Shorr and Papanicolaou (1939) reviewing their 452 treated cases, concluded that there was no danger provided therapy is carefully controlled as in the regimen described above. Novak (1940) considers that it would be carrying conservatism and caution to the extreme to withhold these substances merely because of possibilities of a purely theoretical nature. However, Auchincloss and Haagensen (1940) disturbed by the probability that these substances may have been a contributing cause of the breast carcinoma which developed in their patient and calling attention to the fact that the stimulus to breast growth which the estrogens exert is as evident in human beings as in laboratory animals, list the following circumstances under which they believe these substances should not be used: (a) in large or prolonged doses, (b) when there is a family history of breast cancer, (c) without initial and repeated clinical examination of the breasts, (d) in patients with chronic mastitis, carcinoma or any form of breast neoplasm, either before or after surgical or radiation treatment.

Disagreeable Reactions to Stilbestrol—In their thorough study of this agent before it was released for commercial distribution Shorr *et al* (1939) found that in 80 per cent of their series of 44 patients its use was associated with toxic symptoms in the form of nausea, vomiting, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, an acute psychotic reaction, and cutaneous rashes. The toxic effects upon the liver and the blood platelets, which sometimes follow enormous dosage in experimental animals, do not seem to have been observed when the drug is used in the human in the therapeutic dosage range (but when the public begins purchasing this agent on its own responsibility at the corner drug store, the possibilities seem to me appalling!). As a matter of fact recent reports such as those of Payne and Muckle (1940), Sevringhaus (1941), Schwittay (1941) and Taylor and Thompson (1941), are mentioning only gastro intestinal reactions, which are alleged to subside under adjustment of dosage, though the last named authors had 1 patient in their total of 39 in whom nausea, vomiting and diarrhea were so severe that use of the drug had to be abandoned.

OBESITY AND MALNUTRITION

OBESITY AND MALNUTRITION

OBESITY

Here I am concerning myself solely with the commonly encountered state of overfatness which is unassociated with any recognizable endocrine dyscrasia. To Newburgh, who has given much thought and study to this matter, the cause of such obesity is simply overeating, indeed, that obese individuals do overeat though they may deny the impeachment, has been shown. For example, Strang and Lvaas (1930) allowed a group of new patients, who considered themselves small eaters, to take for three or four days exactly what they ordinarily ate at home, 8 of the 13 individuals averaged an intake of 2570 calories, though they were obviously more abstemious than when at home, since they lost an average of 2 pounds each. Kisch's (1937) patients were even more gluttonous: 46 of the 50 consumed food with a value of 2000 to 3500 calories, and 28 of 30 who were fed 200 calories in excess of their basal requirements while lying in bed complained that they were not receiving enough to eat. It would seem that those who argue that obese individuals are not obese because they like food too well are losing their case, for the contention that the overeating is due to a faulty metabolism which requires the excessive storage of water and salts and fats is not substantiated in the metabolic studies of Bruch (1940) and others. There seems, however, to be a strong factor of heredity in obesity, indeed, even the tendency to develop peculiar types of obesity (i.e., fatness of certain portions of the body) is directly transmitted. I recall a case seen in Bauer's clinic in Vienna: a woman who had been elsewhere diagnosed as having pituitary disease on the basis of the x-ray finding of some sort of growth in the intrasellar space plus the typical "girdle" distribution of fat, and in which wider investigation showed this type of distribution to have been certainly inherited, since several other normal members of the family were similarly afflicted. Bauer, who has now become a citizen of the United States, expressed the feeling in 1941, that the adipose tissue of an obese person may differ from that of a normal person in having a greater tendency to accumulate fat.

Overweight is a matter deserving serious attention for the following reasons: it predisposes to a number of diseases, particularly diabetes mellitus, gout, cholelithiasis, hypertension and arteriosclerosis, it greatly lowers the resistance against infectious diseases, it greatly increases surgical risk, and it causes considerable inconvenience and even suffering to its victims. It is a strange fact that in all the prehistoric sculptures, and well up into the definitely historical Sumerian and Egyptian periods, the female figure is always shown as grossly obese and the male as slim and athletic. I wonder if the usual explanation of this, i.e., that it indicates the sedentary life of the women of those times, is entirely correct, could it not also be that for reasons almost as inscrutable as those obtaining today the canons of art of the time rigidly proscribed all other depiction?

THERAPY

Principles—In obesity, in addition to stored water, the bulk of the excess weight consists in stored fat, which can only be got out of the tissues by causing it to burn. That is to say we must deny food to the patient so that he will live off the surplus in storage. Starvation would be the ideal but for the fact that under such conditions there occurs depression of metabolic activities sufficient to defeat our purpose. The treatment must therefore consist in supplying what one might call a small air draft of food in order to keep the fat fire in a good glow of burning.

Basic Constituents of a Practical Reducing Diet—Of the many rigid and theoretically perfect diet schemes offered in the literature it seems to me that the one which Bauman has been using for some years at the ambulatory obesity clinic of the Presbyterian Hospital in New York City, most nearly suits the requirements of general practice. It supplies a basic diet of 70 Gm protein, 60 Gm fat and 100 Gm carbohydrates, equivalent to 1220 calories. This constitutes a caloric reduction of at least 50 per cent which is not nearly so radical as the reduction attempted by some other workers but the chances of having this diet adhered to are probably proportionately greater.

Actual Menus of the Practical Reducing Diet—The food is apportioned as shown below (for lists of percentage fruits and vegetables, see Diabetes)

Breakfast—One-half grapefruit or one moderate-size orange or apple or $\frac{1}{2}$ cup of strawberries, 2 eggs, coffee or tea with $\frac{1}{2}$ cup of milk, saccharin, and 1 thin slice of bread.

Lunch—1 Five per cent vegetables, 2 cups, 1 egg, 1 medium size orange or 1 apple, tea with 2 tablespoonfuls of milk.

2 Five per cent vegetables, 1 cup, 10 per cent vegetables, $\frac{1}{2}$ cup, 2 eggs or $3\frac{1}{2}$ ounces (100 Gm) of broiler with 2 teaspoonfuls of butter, 1 medium size apple or orange or 1 cup of strawberries, tea.

3 Five per cent vegetables, 1 cup, 10 per cent vegetables, $\frac{1}{2}$ cup bread, 1 thin slice, meat, $1\frac{1}{2}$ ounces or cheese, 1 ounce, $\frac{1}{2}$ cup of milk and custard sweetened with saccharin.

Dinner—1 Meat or fish, $4\frac{1}{2}$ ounces (140 Gm), 5 per cent vegetables, 1 cup, 10 per cent vegetables, 1 cup, 1 medium-size orange or 1 cup of strawberries, tea.

2 Meat, 3 ounces (90 Gm), 5 per cent vegetables, 1 cup, 10 per cent vegetables, $\frac{1}{2}$ cup (some of the vegetables may be used as salad, vinegar and liquid petrolatum being used as dressing), bread, 1 thin slice, 1 medium size apple or orange, tea.

3 Meat, 4 ounces (120 Gm), 5 per cent vegetables, 1 cup, 10 per cent vegetables, $\frac{1}{2}$ cup, 1 small baked potato, $\frac{1}{2}$ grapefruit or $\frac{1}{2}$ cup of strawberries, tea.

A More Drastic Diet—Typical of the more rigorous restriction sometimes employed is that resorted to by Shurt (1939) in reducing his patient from about 400 pounds to about 160 pounds in approximately 18 months. 70 Gm protein, 20 Gm fat and 35 Gm carbohydrate, calories 600, vitamins in concentrated form.

Milk and Banana Diet.—On the grounds of simplicity, low cost, ready availability, palatability, high satiety value, low salt content, and demonstrated effectiveness in securing weight reduction, Harrop (1934) offers a

basic diet of milk and bananas, which he uses in alternating periods of strict and less restricted dieting. The bananas must be fully ripe, *i.e.*, yellow skin flecked with brown, even green tipped bananas will reach this stage quickly at room temperature.

Period of Strict Diet—Six large bananas and 1000 cc of skimmed milk to be eaten in three or more meals according to habit. Useful addition at one meal salad of $\frac{1}{4}$ medium sized head of lettuce, or equal quantity of cabbage, with small amount of mayonnaise made with liquid petrolatum. Continue this diet for ten to fourteen days and expect 4 to 9 pounds loss in moderately active persons. A 4 banana diet, tolerated by some patients, will accomplish even more. Fluids without food value are not only freely permitted but 1500 cc in addition to the milk must be taken.

Period of Less Restricted Diet—Substitute 1 or 2 eggs, boiled, steamed or poached, salted, with $\frac{1}{4}$ square of butter for one or two bananas as the case may be. Continue the milk (occasionally whole instead of skimmed) but add as much 5 per cent vegetables as desired, 1 square of butter may be melted and poured over the vegetables at one single helping only. Condiments without food value, including vinegar, as desired. Allow one small portion of any lean meat—fish or poultry, except pork, no thickened gravy is to be used. Continue this diet for two weeks, expecting no loss or gain, and then revert to the strict diet for two weeks, and back again to this less restricted diet for one week—continuing this alternation until the desired loss is achieved.

Six large bananas and 1000 cc of skimmed milk supply 182 Gm carbohydrate (enough to protect against ketosis), 4 Gm of fat (which is exceedingly low), and 44 Gm of protein. The latter is much below the usual standard of 0.75 to 1 Gm per kilogram of body weight, but only a few of Harrop's patients lost nitrogen (only a small amount) while following this regimen.

Water—The most usual custom is perhaps to restrict somewhat the water allowance below that which is normal, but it is doubtful if this serves any very useful purpose provided the patient is not allowed to gorge herself on water during the periods of greatest weight loss (see below). There are physicians however, who stoutly maintain that water restriction is of great value in that as water is withdrawn from the tissues the other deposited substances are carried with it. The use of diuretics is even sometimes recommended.

Weight Loss—Strang *et al* (1929-1932) felt that in one week there can occur a loss of no more than $4\frac{1}{2}$ pounds of actual tissue. They thought that the much larger weight losses often seen at the beginning of a dietary period are chiefly due to water shifts for which there must inevitably be compensation at a later time, since the early tissue losses are accompanied by considerable dumping of water out of storage. This water is later taken up and at another time let go again, such shifts occur throughout the dietary period, but the steady loss of fat tissue is going on all the while even though as is so often discouragingly observed, the patient actually gains weight (weight in water, according to this reasoning) though eating the lowest possible quantity of food.

Short's patient, above referred to, lost an average of 12 pounds per month in the beginning, he says that in his experience reductions of 10 to 20 pounds a month over considerable periods have not been attended by any untoward

symptoms Gray and Kallehach (1930) find that smaller losses of 4 to 8 pounds do not predispose to wrinkles and irritability Of Bouman's 183 patients on the slower (practical) method, who averaged 54 pounds over weight in the beginning, after an average of about ten months treatment, 67 had lost 10 pounds or less, 33 from 10 to 15 pounds 16 from 15 to 20 pounds 15 from 20 to 25 pounds and 27 more than 25 pounds

Subjective Changes—Straag's experience accords with that of all who have succeeded in gaining the cooperation of obese individuals sufficiently to obtain results One is astonished at the unanimity with which patients reported a return of vigor, a feeling of well being and resistance to fatigue which had been lost for months or years A great variety of obscure symptoms and minor ailments disappeared " Headache and difficulty in breathing usually disappear very rapidly, and as a whole the symptomatic improvement exceeds what can be accounted for by the relief from the mechanical burden of only a relatively few pounds Menstrual disturbances often strikingly improve

Exercise—Tennis golf, and horseback riding are favored for those who can afford them Swimming is very excellent because of the added energy loss incident to the prolonged cooling of the body surface, but it should be noted that the reducing value of any exercise is lessened as soon as skill is acquired Bauman advises the daily walking of 2 miles in forty five minutes or less or calisthenics lasting ten minutes morning and night, he finds that ordinary housework does not replace systematic exercise Strong and his associates are skeptical of the value of exercise maintaining that routine calisthenics do not make up for the increased food intake as a result of the stimulation of appetite They feel that the individuals who most need rapid weight reduction because of impending exhaustion of the circulatory apparatus after years of chronic strain upon it are the very ones in whom the genuine work necessary to accomplish a real loss of 300 to 400 calories cannot be permitted

Thyroid Therapy—The contention that thyroid substance should be given not in the sense of supplying a deficient internal secretion but rather to speed up metabolism so that the stored materials can be utilized better when food is withheld has been attacked by Straag as being irrational if not actually dangerous Though the basal metabolic rates of his obese patients fell within normal limits for their actual size and weight, they were much above normal if computed upon the basis of ideal weight For instance a woman, aged forty-one, whose ideal weight was 133 pounds actually weighed 210 pounds Her basal metabolic rate was minus 4 in relation to her actual weight but plus 23 in relation to her ideal weight ' In other words this patient as for as her real self, her active useful tissues was concerned was operating at a level 27 per cent higher than was normal for her ' Such levels of metabolism would normally be associated with thyrotoxic symptoms and if they really supply an index of the increased work being done by the obese is merely living the further whipping up of the rate with thyroid substance should certainly be approached with full caution Bulger (1930) makes the point that in the obese adolescent especially the drug should not be used since we do not know ' to what extent such tinkering may upset neuro-endocrine equilibria ' Bruch (1931) makes the comment that in order to obtain a stimulating effect on the metabolism much larger doses are needed than are generally given to obese patients he says that the claims for the specific value of thyroid substance

in the treatment of an obese child can frequently be discarded on the basis of insufficient dosage alone. Short says he finds thyroid not well tolerated in the beginning during the period of increased metabolism, but as the metabolic rate falls under the influence of the reducing diet he says he uses it with consistently good results. However, Andersen (1940) reports in detail 8 cases of very severe thyrotoxicosis in women past the climacteric in which he believes the excessive use of thyroid substance in weight reduction was responsible.

Other Drugs—Bram (1940) has proposed the use of *digitalis* leaves, 1 to 2 grains (0.06 to 0.12 Gm.) three times daily at meals, to reduce the appetite; this seems to me a drastic step to take for *digitalis* is a very potent agent. Greece (1940) has used the tincture of *belladonna*, alone or with a sedative in a small series of cases, in quite a large proportion of which the appetite was reduced; this is another potentially toxic agent. The most recently proposed agent is *benzedrine sulfate*, which is also not only a very potent drug but one to which patients may apparently become addicted. Ersner's (1940) recent report on this drug is an enthusiastic one because apparently in most of his "more than 500 cases" the loss of appetite consequent upon taking the drug made dieting easy. He offers no records of basal metabolic studies but says these records show very little change under the drug; in most instances constipation seems to have been induced and often there was a great deal of premenstrual tension, irritability and lightheadedness in the beginning. Ersner began with a single daily dose of 1 tablet of $\frac{1}{2}$ grain (10 mg.) and consumed more than three months in reaching the full dosage of 1 tablet after each meal; the one daily dose was given for the first month, followed by a rest period of a week, then the preceding dosage was given for a week before proceeding to the use of 2 tablets, and the final dosage was reached by the same process. *Dinitrophenol* should be used under no circumstances whatsoever for there is ample proof of its highly toxic nature.

Contraindications to Drastic Dieting—These are felt to be the presence of a tuberculous lesion, myocardial disease, and advanced cardiovascular renal disease. Some observers feel that nevertheless some effort should be made in all cases of gross obesity to aid the patient to cope with his major disease by at least gradually reducing his weight. Adolescents and the elderly, who are thought to bear reduction measures poorly, have been treated by the drastic diets of Straag and his associates without the occurrence of any untoward incidents.

MALNUTRITION

Malnutrition is seen in individuals who are unable to obtain sufficient nourishing food to prevent semistarvation, in those who suffer from faulty utilization of food as the result of some circumstance such as vomiting, pylorospasm, diarrhea, etc., and in cases of pituitary cachexia, which is an extremely rare condition. In addition there are the cases with which I am dealing here, undernourished individuals who usually fall into one of the following three main types: those who are just "naturally" thin,

those who have lost much weight during a period of excessive physical or mental strain or illness and have subsequently failed to regain it, and those girls or young women (occasionally a young boy) with anorexia nervosa, in whom, as well stated by Ryle (1936), "a psychic trauma or a foolish habit or some combination of the two results in a loss of appetite and a suppression of the menses" In all, the difficulty lies in the possession of a subnormal appetite, for it has often been shown that there is nothing at all to prevent these patients from putting on weight if one can only induce them to eat enough

THERAPY

Stuffing Diet—The dietary scheme which served Ralli and Brown (1933) well is here given in the form of a table (Table 18) Their patients gained an average of 17 pounds in six weeks on this diet Once the initial repugnance for excessive amounts of food is mastered, patients usually eat with relish and after a while retain an improved appetite without special effort Ralli and Brown's patients averaged a daily caloric consumption of 4000 to 4040, the diet provides a total of 5060 But not all patients can be induced or can force themselves with the best of will, to cooperate fully in this stuffing campaign

Egg-yolk Powder—Steiner (1941) reports 10 patients ill of rheumatoid arthritis or of nephritis, hospitalized for long periods and either not gaining or even losing weight on a well balanced diet of 2600 to 3000 calories, 9 of the 10 gained an average of nearly 10 pounds during an average period of about eight weeks as a result of adding to the diet daily 100 Gm of egg yolk powder, suspended in milk with vanilla and sugar added to taste The 100 Gm of powder were said to supply 67 Gm of fat, 22 Gm of protein, and 620 calories

Insulin—In a usual dosage of 5 units three times daily, twenty minutes before meals, Higgons and Ostlund (1934) found insulin of value in under nourished children who do not respond satisfactorily to the usual hygienic and dietary treatment, but of no value in those already gaining, they found very young children frequently thrown into hypoglycemic shock Brain (1940) also thinks it a valuable agent in children as well as in adults In Blotner's (1938) series of 100 adults improvement in appetite (some of the patients became voracious eaters), in the sense of well being and in physical and nervous strength, was a marked early and persistent effect These patients were all ambulatory and all normal physically except for the moderate to severe malnutrition They ordinarily injected 10 units of insulin three times daily about twenty minutes before meals, but some took it only twice a day and in a few instances the dose was increased to 20 units two or three times daily The injections were usually taken for one to three months, the shortest period being two weeks and the longest seven months Of course a liberal diet was advised In most cases the weight gain was 3 to 4 pounds per week for the first two or three weeks, but it became less marked with the passage of time and finally remained constant regardless of the continuance of insulin The average total gains in those who persisted in the treatment for one to four months were 10 to 15 pounds Blotner finds that the majority of this group of patients have maintained the increased weight during various follow up periods, some as long as four to six years However, in Nichol's (1932) series of 42 patients, 31 maintained their gain for six months or less

TABLE 18.—DIET FOR THE UNDERNOURISHED PATIENT (RALLI AND BROWN)

	Amount	C.	P.	F.	Cal.
Breakfast					
Cereal	1 oz.	23	5	0	104
Cream	2½ oz.	2	2	20	126
1 glass milk	8 oz.	12	8	9	161
Egg	One	0	6	6	78
Bacon (crisp) strips (use fat for egg)	1 oz.	0	5	19	135
Banana or prunes	2½ oz.	20	1	0	84
Orange juice	2½ oz.	20	1	0	84
Butter	1 oz.	0	0	25	225
Bread	2 slices	54	0	0	252
Jam or jelly (2 heaping tablespoonfuls)	1 oz.	30	0	0	120
Sugar	2 t.	40	0	0	160
Coffee	1 cup	0	0	0	
At 10 A.M.		201	35	79	1647
Cocoa malt with 1 egg and cream or 8 oz. milk with 1 egg and cream	1½ glasses	40	19	56	560
Lunch					
Meat-fish-chicken	2½ oz.	0	20	20	260
Potatoes-rice-spaghetti	2½ oz.	20	2	0	88
Salad (Mayonnaise)	1 t.	0	0	18	135
18 per cent fruit—4 lettuce leaves	2½ oz.	15	1	0	64
Bread (1 oz. slices) or 1 large roll	2 slices	50	5	0	168
Vegetables, 5 per cent	2½ oz.	8	1	0	13
Butter	1 oz.	0	0	25	225
Dessert (Pie, Puddings or custard, Ice cream)	2½ oz.	20	4	4	152
At 4 P.M.		194	25	100	1648
Cocoa malt with 1 egg and cream (½ glass) or 8 oz. milk w 1b 1 egg and cream	1½ glasses	40	19	56	560
Dinner					
Meat (2 oz. cheese or 2 eggs)	2½ oz.	0	20	20	260
Potatoes or a creamed vegetable	2½ oz.	20	2	0	88
Butter	½ oz.	0	0	12 5	112
Bread (2 slices, 1 oz. each)	2 slices	50	5	0	168
Vegetables, 10 per cent	2½ oz.	8	1	0	23
Dessert (same as noon)	2½ oz.	20	4	4	152
Night Meal 10 P.M.		152	37	70 5	1549
Vegetables for sand	2½ oz.	5	1	0	16
Bread	2 slices	50	5	0	168
Mayonnaise or butter	½ oz.	0	0	5	72
Milk	1 glass	12	8	3	161
or		31	15	17	417
Hersey bar (10-cent bar)	One	53 5	5 3	24 5	598
Substitutions					
Noon					
Bread	(4 oz.)	72	12	0	356
Mayonnaise or butter	1 oz.	0	0	30	270
Meat (ham salmon or chicken)	2½ oz.	0	20	20	260
or					
Cheese	2 oz.				
Cocoa malt or egg malted milk	1½ glasses	40	13	56	560
Bananas or 20 per cent fruit	Two	40	3	0	168
Supper		152	35	86	1594
French toast					
Bread	2 slices	54	5	0	252
Eggs	2	0	12	12	156
Butter	1 oz.	0	0	25	225
Milk	½ c.	5	3	4	68
Sugar	2 t.	30	0	0	120
Jam or jelly	2 t.	30	0	0	120
Cocoa malt or egg malt milk	1½ glasses	40	19	56	560
		159	44	77	1501

Total calories for all meals 5060

and only 4 kept it for three or four years. Blotner points out that his cases were treated in Boston, Nichols in southern Florida, which may account for the difference in his opinion.

Some observers have found that by no means the majority of a group of patients on whom they have tried this therapy have responded. Dorst (1938) studying the matter in Cincinnati has found that patients exhibiting a low flat glucose tolerance curve are not infrequently encountered in his clinic. A number of such individuals have responded with gain in weight and in sense of well being when placed on insulin therapy. However, one must always be on guard—Treyberg (1935) felt that such improvement as resulted in his cases came from the suggestion accompanying the insulin injections. I have not yet seen the report of a satisfactorily controlled study of insulin therapy in malnutrition.

Special Features in Anorexia Nervosa —Psychotherapy—The principles may be summarized from Pardee's (1941) excellent presentation, as follows: (a) Separate from parents and while in hospital explain thoroughly the father and mother relationship as well as patient's own emotional drive toward sex and the ego. (b) Try to effect realization of the ways in which the patient's failure to meet the issues of life brought on the illness. (c) Prove to the patient that she has no organic disease and that the ingestion of particular articles or quantities of food is no more harmful than others. (d) Do not attempt to induce feeding by coercion.

Danger of Edema—In some desperate cases in spite of the preceding injunction forced duodenal feeding is necessary as a life saving measure and dextrose saline solution may be given intravenously also for the patient is often dehydrated. It is well however, to heed Evans and Shulman's (1940) warning against too free administration of salt and water in cases of malnutrition in which there is likely to be a state of relative hypoproteinemia. Massive water logging of the extravascular tissues including pulmonary edema, can suddenly supervene in such cases.

Thyroid Substance—Some observers, such as Berkman (1939), feel that thyroid therapy is to be tried in the hope that the speeding up of metabolism will be accompanied by increase in appetite, but Cross (1930) believes it is more likely to retard weight increase than to prove beneficial. Richardson (1939) reports a case in which its use was accompanied by an alarming acceleration in the loss of weight.

Vitamins—McCullagh and Tupper (1940) say they routinely add vitamin preparations by mouth and have recently been using thiamine hydrochloride (B_1) and liver extract intramuscularly.

Special Features in the Thin Youngster—Summarizing Bram (1940), the therapeutic approach should be the following: (a) Attempt to retrain the stomach to receive and digest food by feeding small quantities many times throughout the day until the eating habit is reestablished. (b) Psychotherapy is important. Less blame and more praise from the parents, and a simple unpatronizing explanation of calories, nutrition and health from the physician are the most helpful approaches. (c) Enforce improvement in sleep habits, i.e., stress that hours spent in the bedroom should actually be hours in bed and asleep. (d) Supplementary vitamins and hematinics will be indicated in some cases. Bile salts 3 to 5 grams (0.2 to 0.3 Gm.) at mealtime, sometimes increase appetite and reduce flatulence. Insulin is often useful.

DISEASES OF THE GASTRO INTESTINAL TRACT

DISEASES OF THE GASTRO-INTESTINAL TRACT

STOMATITIS

Herpetic Stomatitis—The studies in recent years of Black (1938) Dodd *et al* (1938), Woodhurne (1941), and Scott and Steigman (1941) make it imperative now to recognize as a single entity an acute infectious gingivo-stomatitis which is caused by the virus of herpes simplex and embraces the maladies formerly separately recognized as catarrhal, aphthous and ulcerative stomatitis. In the primary attack usually in infants and young children the clinical picture is usually characterized by systemic infection with fever and irritability, and by soreness of the mouth, red swollen gums, oral fetor, and regional lymphadenopathy. In some cases none, in others a few, and in still others many diffuse small ulcerations may appear anywhere in the mouth. In most instances the constitutional symptoms disappear in a few days but the oral lesions often persist for some days or a week longer. According to this new conception of the disease the well known 'canker sore' of children or adults, which occurs without other involvement in the mouth and without constitutional symptoms, would merely be evidence of recurrent local attacks of this virus in individuals who had already won constitutional resistance through the primary attack.

The primary attacks of herpetic stomatitis tend to occur in family outbreaks and among people who are malnourished though to be sure no direct relationship of this malady to undernutrition has been traced.

One should remember that pemphigus erythema, multiforme dermatitis, herpetiformis, lupus erythematosus and lichen planus sometimes appear in the mouth. It is thought that in a few cases electrogalvanism from dissimilar metallic dentures has caused oral ulceration.

Gangrenous Stomatitis (Cancrum Oris, Noma)—This type of stomatitis is very horrible, but fortunately occurs rarely and then almost exclusively in young children who have been debilitated by a severe bout of illness, a few institutional epidemics have been reported however and Eckstein (1940), having gone to Turkey from Germany, is to his surprise seeing many cases there. Beginning as a small ulcer on the mucous membrane of the cheek, lip or gum, a spreading gangrene rapidly destroys a large portion of one side of the face, death nearly always results in from one to five days. The alleged causative role of the Vincent organism in these cases has never been proved perhaps some of them are really atypical fulminating agranulocytosis. Eckstein feels that noma is probably a toxic form of severe herpetic (ulcerative) stomatitis.

Parasitic Stomatitis (Thrush)—This malady, which is caused usually by the hyphomycete *Oidium albicans*, more rarely by a number of other and quite dissimilar fungi, occurs sporadically and sometimes epidemically among nursing infants. It is generally considered to be due to contamination from imperfectly sterilized nursing bottles or nipples from the introduction of uusterele cleansing solutions into the mouth and from the mothers' breasts or from the hands of attendants. Premature weak athreptic infants or

those suffering from other infectious diseases, are especially predisposed to thrush, but it may also attack otherwise healthy infants. The lesions consist of small gray white or yellow brown patches, somewhat resembling milk curds, scattered over the cheeks, gums, lips and tongue, their removal, which is difficult, leaves a slightly bleeding area. Examination of one of these crushed "curds" reveals the organism. The attack usually clears up in two or three days, but hospitals fear thrush because an epidemic not infrequently fails to yield even to vigorous treatment, and without treatment may run a course of several weeks. Very rarely generalized systemic invasion occurs.

Mercurial Stomatitis—The first symptoms are metallic taste and soreness of the teeth upon chewing, then the gums become spongy, swollen and tender, and they bleed very easily, the breath is quite foul and the salivary glands are swollen and tender. In extreme cases ulceration, loss of teeth and even necrosis of the bone may take place.

Bismuth Stomatitis—This type of stomatitis is characterized by a blue black line along the margin of the gums, soreness of the gums, salivation, and in severe cases ulceration.

Vincent's Angina—See among the Infectious Diseases.

THERAPY

Herpetic Stomatitis—During the attack, the soft foods, such as milk, slightly cooked eggs, soups, custards etc., are the only foods that adults can take with any sort of comfort. The feeding of infants sometimes becomes quite a difficult problem. Local treatment consists in the use of mouth washes such as the following: tincture of myrrh, 1 part to 25 or 50 parts of water; potassium permanganate 1 part to 8000 parts of water, or some such mixture as the following, which is a very satisfactory mouth wash.

R. Thymol (saturated solution)	3ij	61 0
Hydrogen peroxide	3ij	61 0
Glycerin	3ij	61 0
Potassium chlorate (saturated solution) to make	3viij	250 0
Label Dilute and use as mouth wash.		

In infants, who cannot of course gargle or rinse the mouth, it is necessary to apply these washes on a cotton swab. The saturated solution of boric acid has long enjoyed a reputation as the ideal mild mouth wash, a reputation entirely undeserved for the reason that it is practically worthless as an antiseptic.

In recurrent "canker sores" the silver nitrate stick is very effective. It should be firmly applied to the bottom and sides of each of the ulcers, rinsing the mouth with water afterward if the caustic and metallic taste is very objectionable. In more diffusely ulcerated cases the use of potassium chlorate to be swallowed is recommended by several physicians of wide experience, despite the well known ability of this drug to cause methemoglobin production, it is excreted partially through the salivary glands and thus the ulcerated surfaces in the mouth are continuously bathed in a potassium chlorate solution. Bradbury states that the drug is almost a specific when used internally. He recommends for an adult, 10 grains (0.65 Gm.) three times a day, to be taken well diluted for a child of six years 3 grains (0.2

Gm) every four hours. Wise and Parkhurst recommend 20 grains (1.3 Gm) three times daily for the adult.

In recurrent cases, Woodburne (1941) has successfully employed the repeated vaccination method of treatment. Smallpox vaccination is performed at intervals of one to two weeks unless a 'take' occurs in which case the reaction is allowed to subside before vaccination is again performed, in Woodburne's series vaccination was performed twice in 3 cases, three times in 2, four times in 5, five times in 4, six times in 2, seven times in 2, eight times in 3, fifteen times in 1.

Gangrenous Stomatitis—Very rarely early and radical excision of the gangrenous area without consideration of the cosmetic effect will stop the process, fuming nitric acid and actual cautery have practically no successes to their credit. Tauber and Goldman's (1936) case in an adult progressed rapidly to a fatal termination despite the use of neosarsphenamine systemically (fusospirochloa organisms had been found in the lesion) and the following agents used locally: sodium perborate, hydrogen peroxide, potassium permanganate, mapharsen, sodium ricinoleate solution, bismuth paste and benzoyl peroxide powder. Of Eckstein's (1940) 9 patients treated with neosarsphenamine 8 died, but of 21 treated by local injections of "antigangrene serum" into the healthy surrounding tissue, 11 progressed to complete recovery. Eckstein believes the action of the serum to be nonspecific. McMillen (1941) reports 7 cases that were astonishingly arrested by the daily application of full strength formalin, neither sulfanilamide nor sulfapyridine proved useful in these cases.

Parasitic Stomatitis—Nothing new has developed in the treatment of thrush in a good many years. Faher and Clark (1927) in a careful report of an epidemic in newborn infants, wrote as follows:

"The treatment of a patient who has thrush may follow one of two lines: simple cleansing or the use of antiseptics. For the first, alkaline, but not too alkaline, solutions frequently applied to the mouth may result in cure after a week or two, especially in healthy infants and in infants with mildly virulent strains of *Oidium* [2 per cent sodium bicarbonate solution—H. B.]. The outcome of such treatment is, however, always problematic, and against relatively virulent strains such as we have often seen, is practically certain to be disappointing. Boric acid is not only valueless but, as the recent experience in Chicago demonstrated, dangerous. We emphasize the point because a recent text in a book on pediatrics recommends the Escherich boric acid sac or teat. This is a small sac of silk or catgut filled with boric acid powder sweetened with saccharin which is placed and left in the infant's mouth, presumably until the thrush is cured. It is possible that boric acid poisoning might result from such treatment. Solution of liquor formaldehydi has never given us satisfactory results, and we believed that the reason is its poor penetration and its rapid dilution by the secretions of the mouth below the point of disinfecting efficiency [1 per cent solution of formalin is usually used—H. B.]. With mercurochrome 220 soluble we have obtained occasional but not constant retrogression of the oral lesions [1 to 2 per cent aqueous solution—Faher and Dickey (1925)]. With gentian violet we have obtained better and more constant results than with any other substance. To obtain them, however, it is necessary to follow certain rules. Treatment should be given at least one hour after feeding. The mouth should be gently cleansed

with several cotton swabs to remove the adherent mucus over the affected areas—a most important precaution, since as Churchman has shown, the dye is absorbed and its therapeutic effect on the lesion annulled by overlying secretion. The dye, in 1 per cent aqueous solution, must be freshly prepared (not more than a few days old) and must be applied generously, first to the affected area and then over the tongue and in the buccogingival folds. The treatment must be repeated once or twice daily for at least three successive days, and, if possible, every other day thereafter for from one to two weeks. The mother's breasts should be carefully cleansed with soap and water before each nursing, and the first few drops of milk discarded to prevent reinfection.

"If this technic is followed, the lesions will have nearly disappeared by the second day and entirely so by the third, new ones will not appear. If only one or two treatments are given, recurrences will frequently occur, usually in other areas than the site of the original lesion. In spite of the deep staining of the entire oral cavity, which persists for a day or two after treatment has been stopped, there is no apparent interference with the baby's appetite or ability to feed. Stain on the lips or chin can be easily removed with a little alcohol. The stools during treatment often appear purplish."

Abraham's (1926) 33 patients responded favorably to the application of a solution of 2.5 to 3.5 per cent ferric chloride in from two to four days on the average. Higher concentrations produced irritating effects. Animal experiments showed that the virulence of the organism was considerably decreased by the treatment.

Mercurial Stomatitis—This type of stomatitis is infrequent in the patient whose oral hygiene is perfect unless ordinary therapeutic doses of the mercurials are exceeded. After the teeth and gums have been put in as good condition as possible, it is well to employ the potassium chlorate mouth wash (see Herpetic Stomatitis, above) as a routine practice throughout the period in which the mercury is being given. At the appearance of the first sign of stomatitis the drug should be stopped and then only very carefully resumed upon its subsidence. When the stomatitis is only a part of the general picture of mercury poisoning, one must resort to other measures as well (see Mercuric Chloride Poisoning).

Bismuth Stomatitis—See under Syphilis

DYSPEPSIA

(Indigestion)

It is mandatory upon the physician to approach the diagnosis and treatment of every case of dyspepsia by the purely eliminative process, for though it is undeniably true that the majority of digestive complaints are due to either sensory, secretory or motor disturbances, and are therefore functional rather than organic in origin, yet the gravity of the organic lesions when present is so great that they must all be ruled out before the diagnosis of a purely functional dyspepsia is accepted. Granting, then, that this has been

done, i e., that the patient has been shown not to have gastritis, peptic ulcer or cancer, the functional disturbances remain to be considered—provided that two further possibilities are also eliminated, namely, dyspepsia due to dietary indiscretion, and secondary, so-called “reflex” dyspepsia. *Dietary indiscretion* is usually encountered in those of a fulsome habit, who have regard neither for the quantity nor the quality of their food and drink, and who disdain all the decencies of table deportment, occasionally, however, an individual suffering from this type of indigestion will not be one of the gobblers but merely a person who suffers from the taking of small and even well masticated quantities of certain foods, such as fried and greasy dishes, heavy hot breads, excessively hot or cold dishes, etc. Any of the symptoms of indigestion may be manifested, and they will all usually disappear if the offending articles are withheld from the diet, or if the individual is made to curb his gluttony—that is to say, if a silk purse is made out of a sow’s ear. *Reflex dyspepsia* may indicate the presence of gallbladder disease, chronic appendicitis, peritoneal adhesions, epigastric hernia, intestinal worms, cirrhosis of the liver, etc. It should always be borne in mind, as well, that coronary disease sometimes simulates an acute gastro intestinal disease, and that a functional dyspepsia is often associated with disease of the genito urinary organs, hyperthyroidism, the anemias, and pulmonary tuberculosis.

NERVOUS INDIGESTION

This type of dyspepsia whose sufferers are legion, is characterized by the following facts: the gastro intestinal syndrome changes frequently, so that at one time the picture will be dominated by a gastric symptom of one sort and at another time by a symptom of another sort altogether, there are usually other psychasthenic complaints, such as palpitation, poor circulation, fatigue, peculiar forms of headache, etc.; there is no definite relationship between the quantity or quality of food taken and the type and degree of the gastric disturbance, and the symptoms are very dependent upon the state of mind of the individual at the time he partakes of a given meal. The most usual complaints are of fullness and discomfort in the epigastrium, pain, eructation of gas, nausea, vomiting, and difficulty in swallowing. Often the appetite is poor, but sometimes a patient, believing that only by forcing himself to eat will he get well, is given to inordinate performances at table. Others attempt to treat themselves by eliminating articles one after another from the diet in the hope of finding the offending food, such individuals not infrequently maintain themselves in a condition of semistarvation, and affect their malady not in the least unless it be to make it worse.

Psychotherapy—I quote from Alvarez’ excellent treatise on this subject: “The first and often the most important step in the psychic treatment is taken when the physician makes a complete and careful physical, roentgenologic and laboratory examination. If this does not reveal signs of serious disease, many persons immediately lose interest in their symptoms and go away satisfied. Another important factor in the psychic treatment is the taking of a good history, and especially a history that brings out all the details of family and business worries, of domestic infelicity or of the phobias that so often are at the bottom of the trouble. Unless these things are done

it is not only useless but often criminal to tell the patient not to worry. Some consult us simply because they have been shocked by the sudden death of a friend or relative. They fear that they too have cancer or heart disease, but they will not admit it and come complaining of some minor ailment. Especially when dealing with older patients it is often well to say at the close of the examination 'As we examined you we had always in mind the possibility of cancer beginning somewhere, and we are now glad to say that nothing suspicious has been found.'

'Fortunately, much can be done in many of these cases by giving the patient the mental purgation that comes with the pouring out of secret worries into a sympathetic ear. The physician can often help these persons by advising them wisely, and by leading them out of a maze of muddled thought to the point where they can forgive and forget and acquiesce to things that cannot be cured. For years I have kept in my office a copy of Trudeau's autobiography with a bookmark at page 318 in order that I may turn quickly to his remark that he had learned from his patients that the conquest of Fate is not by struggling against it, nor by trying to escape from it, but by acquiescence.' The asthenic person, the person with mucous colitis, or the one to whom nature has given a raw deal can often be made over into a useful and happy member of society if he can be taught this lesson of acquiescence to stop looking for a cure and instead to settle down to get along as best he can with his handicap.

'The next thing in most cases is to see how a rest can be obtained with the least expense and loss of income. If a vacation is taken, it must be one that will bring the patient back better off than when he left. Too often our vacations are of the type that caused the Irishman to remark plaintively, 'How happy we'd be if it weren't for our pleasures.' If a man cannot well leave his business he can often, for a month or two, answer his mail and confer with his assistants in the mornings, and can then spend his afternoons at home or on the golf course. I have seen such excellent results from this type of resting that for business men I prefer it to a complete vacation. The mother with several small children and few resources can also be helped tremendously if she is taught to go back to bed after the children are sent off to school. She may have to continue with mending and sewing but even so, a few weeks of mornings in bed will often work a miracle.

'The sick who are so situated that they must either keep at work or starve can often be taught to hoard their small stock of energy and to live within the limits of their nervous strength. Many tire themselves out by putting too much energy and emotion into trivial tasks. Women in particular must be exhorted to break themselves of the habit of getting all stirred up over little things, and of reviewing at great length painful or annoying experiences which a more sensible person would promptly forget. Others must be taught to go to bed earlier at night and some must for a time retire from leadership or active participation in church, civic or social work. Some can get their grip again if they will only rest in bed on Saturday afternoons and Sundays.'

Oftentimes the physician overlooks the importance of relieving insomnia which can frequently be done by teaching the patient to keep his mind off disturbing thoughts, to avoid mental work or exciting conversation after dinner, to take a warm bath and a little food on retiring and to go to bed

earlier. When these measures fail, Alvarez does not hesitate to use the barbiturates, believing that the opposition of many physicians to sleep producing "dope" is entirely unjustified. The subject of insomnia is separately discussed in a later chapter.

Physical Therapy—Again Alvarez "Many of the weak and partly bedridden patients can be put on their feet literally and figuratively only with the help of an intelligent, cheerful and masterful physical therapist who can build their strength until they can stay up all day. Each day the invalid is given something to do, something to think about, something to hope for and some one with whom to talk. Not all persons, however, are helped by massage. Only those 'pussycats' who love to be stroked will thrive on it, those who are ticklish or who hate to be touched by strangers will be made worse. Stoutly built men who were once athletic but who have since become flabby and fat can often be helped by a course with a trainer. Ultraviolet radiation, in my experience, helps in raising resistance, improving appetite and putting on weight.

"These physical therapeutic measures are invaluable in many cases if only because they keep the patient busy and hopeful and bring him back repeatedly under the influence and guidance of the physical therapist and the physician. They keep him out of mischief and out of the hands of the quacks. One of our biggest mistakes in medicine today is that we have allowed others to monopolize these modes of treatment. One of the great advantages of having the work done under our supervision is that we can be watching the patient, learning more about his troubles, and seeing him on occasions when he has something definite and telltale to show us, like a fever, a point of tenderness, or a tinge of jaundice."

Smooth Diet.—Alvarez feels that the most important dietetic considerations are that the patient be taught to eat again that the diets provided for him be neither too restricted nor monotonous and that the taking of all unnecessary roughage be forbidden. The virtues of the smooth diet he believes to be not in the fact that cellulose is so indigestible and by its presence likely to interfere with the action of digestive ferments on starches and other foods but rather in the assumed existence in the sick individual of areas of reversed peristalsis which fluids will pass but solids will not. To resort in the majority of cases to a milk diet he believes to be unfortunate because milk disagrees with many persons and is bulky and leaves a large residue. If the use of a smooth diet does not bring relief in a few weeks, the case is believed to be one that is not going to be relieved by any form of dietary restriction.

The following are the "smooth diet" instructions often given to patients:

If you are to give this diet a fair trial eat no coarse foods with fiber—skins, seeds or gristle. Avoid particularly salads with celery, tomatoes, cucumbers and pineapple; many of the green vegetables, raisins, berries, jams full of seeds, nuts and many of the raw fruits. Beans, cabbage, onions, green or red peppers, melons, cucumbers and peanuts are notoriously gassy. If you are living in a boarding house you can stick to this diet by simply avoiding the forbidden foods and eating more of the digestible ones which are put before you.

Avoid sugar in concentrated form and take no candy or other food between meals. Hot cakes and waffles might not be bad if they were not eaten with so much syrup. Fried foods are not bad if they are properly fried, that is, totally immersed in fat at the right temperature. Avoid eating when in a rush and when mentally upset. Family rows should be held away from the table. Chewing gum may cause distress, as much air is swallowed with the saliva. Digestion is greatly helped by a good chewing surface. If there are any gaps in your teeth have your dentist fill them with bridges. Purgatives often cause flatulence and distress in the abdomen.

"The following are suggestions for breakfast Orange juice, grapefruit (avoid the fiber in the compartments) cantaloupe and melons are inadvisable Coffee, if desired is allowed in moderation It sometimes causes flatulence If you are sensitive to caffeine try kaffee hag or instant postum Chocolate, cocoa or tea, one or two eggs with ham or bacon (avoid the tougher part of the bacon), white bread, toast or zwieback with butter, any smooth mush such as farina, germea, cream of wheat, cornmeal or rolled oats (a fine oatmeal can be obtained by calling for Robinson's Scotch Groats), puffed cereals and cornflakes are also allowed Shredded wheat biscuits and other coarse breakfast foods are not allowed Bran is particularly harmful Graham bread is permitted but not the coarser whole wheat bread

"Suggestions for lunch and dinner In fruit cocktails avoid the pieces of orange and pineapple Broths bouillon, cream soups and chowder are allowed, also meat, fish or chicken, squab or game, excepting duck (avoid the fibrous parts and gristle) Veal may be tried, it is not digested well by many persons Eat no smoked fish or pork Crab and lobster had better be left alone Oysters and sausage may be tried later

"Bread and butter are allowed and hot biscuits if they are made small so as to consist mainly of crust Rice, potatoes mashed, hashed brown or French fried, are allowed, and later may be added sweet potatoes, hominy, tomatoes stewed, strained and thickened with cracker or bread crumbs, well-cooked cauliflower tops with cream sauce, asparagus tips, Brussels sprouts, squash beets turnips, creamed spinach Italian pastes, noodles, macaroni and spaghetti cooked soft purées of peas, beans lentils lima beans or artichoke hearts All skins or fiber should be removed by passing the food through a ricer Sweet corn may be used if passed through a colander There are practically no other vegetables that can be purged to advantage String beans (large tender string beans which can be used as a vegetable or salad can now be obtained in cans) are allowed if they are young and tender

"No salad should be taken at first Later you may try a little tender lettuce with apples or bananas tomato jelly or boiled eggs Mayonnaise and French dressing are allowed Potato salad without much onion may be tried

"Suggestions for dessert are Simple puddings, custards, ice cream, jello plain cake and canned or stewed fruits particularly pears and peaches Cottage cheese is permissible other cheeses often cause trouble Apple peach, apricot, custard and lemon cream pie may be tried if only the filling is eaten

"In case of constipation stewed fruit may be taken once or twice a day In winter the dried pared fruit may be used for stewing Prunes are probably the most laxative of fruits and if eaten every other morning they will relieve the average case of constipation They should be cooked slowly until they almost go to pieces If the skins are still tough they should be discarded Apple sauce is much more palatable if made from unpared and uncored apples The sauce is strained later It may be mixed with a little tapioca or sago The apples may be baked Apples, even when cooked, often cause distress Blackberries and loganberries can be stewed and strained and the sweetened juice thickened with cornstarch This makes a delicious dish with the full flavor of the berries Later you may try fully ripe pears and peaches

"Make no effort to drink water Be guided by your thirst Avoid excessive use of salt or other seasoning If you wish to gain in weight eat as much cream, butter, fat, and starch as you can If you wish to lose or to stay thin live largely on vegetables, fruits and salads, with a moderate amount of lean meat

Drugs—The use of hypnotics has already been discussed Alvarez believes that those patients who are greatly helped by alkalis will be found to be suffering from ulcer or some other organic disease He has little faith in tonics and hitters and uses them only at times for psychic effect, in such instances preferring such high sounding preparations as 'beef, iron and wine' Strychnine he looks upon as the last drug on earth to give to a nervous person and shares with most other gastro-enterologists a lack of faith in administered pepsin, pancreatin, etc Carminatives are sometimes helpful (see Index for prescription)

PYLOROSPASM

Pylorospasm, unassociated with ulcer or other organic lesion, is a spasmoidic constriction of the pylorus occurring usually at the height of digestion There is pain, which may be very intense, eructations and vomiting, some

times without nausea. A firm protruding mass, indicating the contracted pylorus, may appear in the epigastrium. Vomiting gives great relief, but in many cases the spasms become so frequent that the condition merges into a state of spastic contraction with consequent dilatation of the stomach, the patient can retain no food and of course wastes away rapidly.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter.

Drugs—During the attack a hypodermic injection of $\frac{1}{150}$ grain (0.0005 Gm) of atropine sulfate oftentimes gives complete relief, but this drug is not so infallible in its action here as would be expected considering its well known ability to relax involuntary muscle. Infants are relatively insensitive to it, in pylorospasm, doses of $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.8–2.4 mg) are sometimes used in them with good effect and no significant side actions, though it is certainly advisable to make preliminary trial of smaller dosage.

Machay (1911) reports the cure of the condition in 51, and its improvement in 4 more, of 40 infants given atropine methyl nitrate (eumydrin), dosage 0.5 to 1.0 cc of 1:10,000 solution by mouth twenty to thirty minutes before the six daily feedings per twenty four hours increasing 0.5 cc up to 2.0 to 3.0 cc per dose, even further increases being made if vomiting was not checked.

In 0 of a group of 10 patients Beams (1931) obtained relief with the nitrites—amyl nitrite inhaled from the crushed "pearl," or spirits of glyceryl trimtrate (nitroglycerin) 3 drops on the tongue and increasing the dose by 1 drop every two minutes to effect, or sodium nitrite 1 grain (0.06 Gm) three or four times a day. Eight of the 10 patients who failed to respond to the nitrites responded to atropine given in the form of $\frac{1}{4}$ grain (0.01 Gm) of extract of belladonna three or four times daily, the equivalent dose in the tincture of belladonna would be about 7 minims (0.45 cc), in atropine sulfate about $\frac{1}{150}$ grain (0.015 mg).

Myerson and Ritvo (1936) recommended the use of benzedrine sulfate orally in a dosage of $\frac{1}{4}$ to $\frac{3}{4}$ grain (0.01–0.04 Gm) in pylorospasm since it has been satisfactorily used to relieve spastic gastro intestinal states in routine opaque roentgenoscopy. The drug rarely causes more severe reaction than restlessness if not used too frequently, but it should be charily employed in cardiovascular cases. When an opiate is necessary, morphine or dilaudid should not be used for obvious reasons, combine $\frac{1}{4}$ to 1 grain (0.032–0.065 Gm) of codeine sulfate or phosphate with the atropine.

Dry Diet—Use of a diet that would be difficult to vomit was advocated by Sauer some years ago. The following case report of Speidel is of great interest.

* Z. C., female aged twenty-one, came to my office on September 23, 1923 complaining of general abdominal distress, loss of weight, constipation, poor appetite and vomiting. The onset of these symptoms was gradual and began two years previously about the time she graduated from high school. There was some emotional upset connected with competing for a medal or honors of some sort. All her symptoms had become gradually worse. Vomiting occurs now every time she eats or drinks anything. Upon graduating from high school she weighed 93 pounds. Present weight, 69½ pounds. A Ray studies revealed that barium left the stomach very slowly and that there was marked ptosis of both the stomach and large bowel. She was sent to the hospital and for the first week received atropine sulfate 1/150 grain hypodermically after each meal, the regular hospital diet and daily gastric lavage. Under this regimen no improvement occurred. On

December 5, 1925, the atropine sulfate was increased to 1/100 grain after meals hypodermically and she was given a dry diet, which in this case meant the regular hospital diet without fluids and without gravies, sauces, soup, fruit juices and any other liquid or semiliquid food. She was given water half way between meals in whatever quantity she desired. Improvement began at once. On December 11th, the atropine was administered by mouth instead of hypodermically and the dry diet was continued."

Eleven years after this patient first came under observation, Spedel (1936) reported her as still having to adhere rigidly to the dry diet and atropine. But she is otherwise a normal healthy young woman and has given birth to a normal baby. Interestingly, after delivery she became unable to empty the bladder and obtained permanent relief of this spasm only after mechanical dilatation of the vesical sphincter had been resorted to.

In Infants—In pyloric stenosis in infants it is usually held that immediate operation is indicated but Sauer believes that thick cereal feedings should be tried for a time to see if improvement will not take place, if the vomiting fails to subside in a week or two and the child does not increase in weight and general condition, operation is resorted to, though of course it is advised at once when infants are first seen in a very emaciated unresponsive state. It is of interest to note that in Mackay's (1941) series of patients successfully treated with eumydrin (see above) the only ones which did not respond were those which had a high fluid intake. Sauer's mixture is skimmed milk, 9 ounces, water, 12 ounces, farina or rice flour, 6 teaspoonfuls, dextrimaltose, 3 ounces, boil an hour or more in a covered double boiler until thick. From 2 to 6 tablespoonfuls of this is given six to seven times daily, scraped off a narrow tongue depressor well back in the mouth. Fluid is supplied as 6 per cent dextrose in Ringer's solution by rectum. The nutrient enema (see Index) might well be used here, for an infant, 20 cc. of the mixture per hour, slowly injected from an ear syringe. In some instances repeated blood transfusions have been resorted to with good effect, Thompson and Gaisford (1935) believe it inadvisable to give more than 10 cc. of blood per pound in order to avoid undue stress on the infant's heart. After an average time of five to eight weeks Sauer was able to substitute appreciable amounts of ordinary milk mixtures for a part of the cereal feedings. This nonoperative treatment was effective in 28 of his 35 cases.

Lavage—In an aged patient, in very poor physical condition, Scriver (1931) resorted to the use of the tube and thorough washing out of the stomach twice daily, the patient was saved and became able to retain a diet upon which he gained weight. Subsequent x-ray examination showed disappearance of the previously observed atony. Mackay (1941) obtained no benefit from routine lavage in her series of infants.

HYPERCHLORHYDRIA

This condition, which is more frequent in young and middle-aged persons than in older individuals, is the most common of all gastric disturbances. The symptoms are caused by a more than normal production of acid (not an increase in the relative acidity of the juice) during the digestion of a meal, but it should be borne in mind that a gastric analysis which shows an apparently normal acidity does not necessarily rule out hyperchlorhydria, for the reason that the "normal" acidity of the stomach contents during digestion varies widely, and an individual may actually suffer from the symptoms of

hyperacidity though an analysis indicates the presence of an amount of acid that is below the "normal" for the majority of persons. The cycle of events is quite characteristic. Pain comes on an hour or more after eating, it is usually of the mild pressure type but may be very severe and boring and extend into the back and up into the throat. There is heart burn and eructation of acid fluid, occasionally there is also vomiting of very acid stomach contents which burn the throat and mouth. Light and starchy repasts are more prone to produce an attack than are heavier meaty meals. The patients are often otherwise in good health, have a good appetite, and are in good flesh.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter.

The usual remedy for an attack of this kind is to administer sodium bicarbonate in a dose of 15 grains (1 Gm.) when the pain appears and repeat several times if necessary. The large doses often taken by the layman are not necessary and may even induce the production of more acid, and it should be pointed out that the drug is to be taken in warm, but not very hot, water, for the latter converts bicarbonate into carbonate which may in itself be irritating. The reader is urged to turn to the discussion of the various antacids as used in the treatment of peptic ulcer, for what is there said applies equally here.

HYPOCHLORHYDRIA (ACHYLIA GASTRICA)

Vanzant *et al* (1932), in the examination of 3746 persons, found a steady increase in the incidence of achlorhydria from youth to old age, 23 to 28 per cent of individuals at the age of 60 failed to show free acid on repeated fractional analysis. Pollard (1933) confirmed the findings, using histamine to stimulate secretion, Bloomfield (1940) confirms the earlier workers also, but finds that the decline in acidity is not uniform and steady in all individuals. The symptoms of the condition are usually few because gastric digestion in these cases is vicariously performed by the intestine, as shown by Hines (1933). However, there is sometimes loss of appetite and a sense of fullness after eating. Nausea and vomiting are rare. In a few cases there is severe pain, heart burn and eructations just as in hyperacidity, sometimes, too, periods of diarrhea and constipation alternate. Schindler (1940), with his flexible gastroscope, finds some type of gastritis in surprisingly many patients with hypochlorhydria.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter.

Hydrochloric Acid—Hydrochloric acid may be expected to act in the following ways in cases of hypochlorhydria: (a) as a stomachic, (b) to form acid aluminates and so aid in proteolysis, (c) to release pepsin from the pepsinogen of the glands, (d) to promote an acid medium for the action of pepsin, (e) as an antiseptic, (f) to stimulate pancreatic secretion and possibly gallbladder emptying, (g) to improve tonus and peristalsis, especially that concerned in gastric evacuation, (h) to aid in the solution of insoluble calcium and magnesium salts in the ingesta, and (i) to stimulate secretion of hydrochloric acid. The practice of using acid in these cases has fallen somewhat into disrepute, because many men find their patients cannot take enough to be of significance as replacement therapy. Perhaps the method of using the drug

which Dobson devised a number of years ago should be more generally employed

(a) The U S P dilute hydrochloric acid should be given in as large amounts as the patient will tolerate—as much as 2½ drachms (10 cc) during the digestive period if possible

(b) Instead of employing the continuous sipping method, it is preferable to have acid taken in fractional doses of 30 minims (2 cc) at a time, one such dose in the middle of the meal and the same amount at fifteen minute intervals thereafter for an hour or more, lengthening the intervals rather than decreasing the number of doses if unpleasant symptoms arise

(c) Two ounces (60 cc) of water, grape juice, lemonade, or any other nonalkaline vehicle may be used as diluent for each dose, but the ingestion of other fluids during the meal should be restricted

(d) It may be well to attempt the stimulation of normal acid production by having one meal daily consist almost entirely of carbohydrate, accompanied by the taking of acid as usual. Tests should be performed periodically throughout the treatment to determine whether the secretory mechanism has been reactivated to any degree

It is well to have the acid taken through a glass tube in order to avoid possible injury to the teeth. Huhhard (1931) found it worth while to use also an alkali forming diet in patients who show evidences of systemic acid base imbalance upon prolonged administration of hydrochloric acid. The addition of citrus fruits and green vegetables to the diet will considerably reduce the excessive acidity of the urine

Lemon Juice—Bethea and Claunch (1939) report that 30 cc of lemon juice in 60 cc of grapefruit juice (unsweetened), sipped during the latter half of a meal, is often effective therapy. While in the stomach these weak organic acids of course function as acids though they are so metabolized as to increase the alkali reserve after absorption

Glutamic Acid Hydrochloride—In combination with hydrochloric acid, glutamic acid forms a white powder which, in contact with water, quickly yields hydrochloric acid. The drug may be given in capsules of 5 grains (0.3 Gm) with water. Shay and Gershon Cohen (1936) obtained satisfactory clinical results by the administration of 1 such capsule shortly after the beginning of the meal and another upon its completion, but Wosika (1936) believes that 8 or 9 of the capsules should be taken for best effects. Bastedo (1938) has not found this drug satisfactory

Digestive Ferments—In Dobson's studies, the use of the essence of pepsin and the extract of the gastric mucosa, gastrin (the dose of either of which is from 1 to 4 drachms), seemed to be without value, since in the absence of acid the enzymes are not effective, and when sufficient acid is placed in the stomach the enzymes appear there. This agrees with the conclusion reached by Bastedo a number of years ago, following a study of the answers to a questionnaire submitted to the members of the American Gastro Enterological Association. From this report it is seen that among the members of the American Gastro Enterological Association many do not prescribe digestive enzymes at all, while those who do employ such enzymes confine their use almost wholly to cases of demonstrated or believed enzyme deficiency. It is further noticeable that almost all who prescribe them show no great enthusiasm over the results of their use, except possibly in the case of pancreatin in proved

pancreatic deficiency. The conclusion is therefore inevitable that they are of minor importance in therapeutics."

ATONY

Atony is characterized by a loss of muscular tone, so that the stomach fails to empty itself in the usual time and finally becomes more or less chronically dilated. The victims of this condition are usually nervous individuals who habitually eat inordinate amounts of difficultly digestible foods and drink large quantities of fluids—until the gastric upset occurs, after which they often attempt to subsist on little more than starvation rations. The most common subjective symptom is a feeling of fulness that appears long before hunger has been satisfied, nausea, eructations, headache, and dizziness also frequently occur, but actual pain and vomiting are rare. A characteristic symptom is that food is tasted long after it is eaten. Gastric analysis shows food remnants seven hours or more after a meal, and on roentgenographic examination the stomach is found to be dilated and its peristaltic action impaired.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter, indeed, there is little more to do for these patients than attempt to apply that treatment. The diet should be restricted to easily digestible foods to be taken in small amounts six times a day rather than in three large meals. If either hyperacidity or, what is more usual, hypoacidity exists it should be corrected as outlined in the discussion of these two entities. The use of strychnine, so long recommended, has never been shown to have any value.

INTESTINAL FERMENTATION

The patient troubled with intestinal fermentative dyspepsia complains of distention with gas, abdominal discomfort and pain, and the daily passage of several liquid or semisolid stools accompanied by much gas. The stools are quite acid and show evidence of a marked impairment of starch digestion but a quite normal digestion of fats and proteins, at times there is also an overabundance of fermentative organisms present. The patients are usually otherwise in good health, except for the stigmata of neurasthenia, and are not infrequently asymptomatic for long periods.

THERAPY

Read the treatment of nervous indigestion at the beginning of this chapter. Dietetics—Occasionally these patients are able to identify the particular food which causes their trouble, and when this is eliminated from the diet they remain free from attacks. In all cases a radical dietary readjustment is necessary to bring about improvement and cure. The diet suitable under the conditions is one rich in protein and fat and poor in carbohydrate, vegetables rich in cellulose must also be avoided or at least selected with care. In the beginning of treatment, Althausen (1935) permits a little toast or well-cooked cereal but reduces the intake of sugar to a minimum. The following are totally excluded from the diet: potatoes, rice, root vegetables, dried beans, peas, lentils, cabbage, cauliflower, Brussels sprouts, broccoli, peppers, cucumbers, onions, garlic, pickles, spices, and sweet milk. Meat,

eggs, fish and cheese, the latter preferably, are allowed. Green vegetables must be cooked and purged. Cooked fruit, fruit juices, nuts except peanuts are allowed. There is no restriction of fats. Of course the ultimate aim of treatment is to allow gradually increasing quantities of the prohibited foods until a relatively normal dietary can be resumed.

Lactic Acid—Althausen feels that there is a special virtue in the drinking of buttermilk, but often finds it necessary to build up tolerance by beginning with small amounts and working up in a quart a day. He also uses lactose at mealtimes, beginning with a teaspoonful and increasing to a tablespoonful. In some instances the attempt is made to overcome excessive fermentation by implanting *Bacillus acidophilus* in the colon, this matter is fully discussed under the treatment of Colon Consciousness.

Kaolin and Charcoal—These substances are sometimes used to adsorb gases, bacteria, and toxins, and to coat the intestinal mucosa.

Intestinal Antiseptics—The so-called 'intestinal antiseptics,' salol, beta naphthol, zinc phenosulfonate (zinc sulfocarbonate), etc., are of no value here. However, the decrease in urinary indoxyl sometimes following the administration of a full dose of calomel indicates that this drug has some antiseptic properties, the laboratory investigations of Von Oettingen and Sollmann also point in this direction. It should be given in a dose of 2 to 3 grains (0.13–0.2 Gm.) upon retiring, to be followed by a saline in the morning; such therapy may be repeated once or twice a month for long periods.

Carminatives—The carminative drugs are those which promote the expulsion of gas without in themselves acting as cathartics. They have long been scoffed at by certain therapeutic nihilists, but I believe that many practitioners of long and unprejudiced experience—the gentlemen who have sponsored more than one empirical remedy that has since been rationalized by scientific experimentation—have considerable faith in their virtues. This group of drugs comprises alcohol, capsicum, cardamom, cloves, ginger, mustard, and the volatile oils generally. A very satisfactory carminative prescription is the following:

R) Tincture of capsicum	℥ss	20
Spirits of peppermint	℥ij	80
Tincture of ginger	℥ij	600
Alcohol to make	℥iv	1200

Label: 1 teaspoonful well diluted every half hour until relieved.

I have heard it said that persons who suffer the sort of gaseous distention which wakes them in the night are often quickly relieved by the taking of bile salts, such as decholin in doses of 4 to 8 grains (0.25–0.5 Gm.). I do not know how such relief is brought about, but if it is, it is, I suppose.

GASTRITIS

Acute gastritis is a not infrequent accompaniment of the acute infectious diseases and is one of the outstanding symptoms of poisoning with such substances as the metals, alcohol, acids, alkalis, etc. For the management of this condition reference must be had to these subjects as they are dis-

cussed elsewhere in the book, chronic gastritis however, requires to be separately considered

Chronic gastritis is caused by persistent overeating, by the prolonged ingestion of foods that are digested only with great difficulty, or are taken too hot or too cold, or by the habitual gorging of all meals, or by the excessive indulgence in tobacco or alcohol, especially the latter, or by the prolonged taking of such drugs as the iodides, copalva, salicylates, etc. It also occurs as a symptom of ulcer and carcinoma, and may be associated with such diseases as leukemia, pernicious anemia, nephritis, tuberculosis, and other constitutional diseases. It is also nowadays assumed that gastritis underlies hyperchlorhydria and hypochlorhydria, so that these conditions may ultimately lose their clinical identities through being merged in the gastritis syndrome. Heart, kidney and liver affections cause passive congestion of the stomach mucosa and ultimately chronic gastritis. Pathologists who have investigated the matter have felt that, whatever the cause of the condition, there occurs a gradual destruction of the glandular apparatus, though this may be preceded by a period of hyperactivity. However, one must bear in mind that such studies will always be embarrassed by the fact that the normal histologic appearance of the gastric mucosa is none too well known. A very promising approach to the subject is that being made by Schindler and his associates who, as a result of their observations with the flexible gastroscope, are classifying cases into superficial, atrophic, and hypertrophic types.

The symptoms are variegated and are such as may occur in any of the dyspepsias. Diagnosis is often difficult, but early morning vomiting of mucus and the finding of large quantities of gastric mucus in the stomach after a test meal, or after a short period of fasting, are very suggestive symptoms, as are also the findings with the gastroscope referred to above.

THERAPY

Diet—Dietary treatment is essential in these cases. Of course the offending food or drink, if it can be identified, must be absolutely eliminated, and then a very simple dietary regimen must be instituted with the hope of gradually bringing the patient back on to a full and normal diet. Eusterman (1936), of the Mayo Clinic, finds that the smooth diet employed in nervous indigestion, or the dietary regimen of peptic ulcer, is equally acceptable.

Lavage—Lavage is very helpful, especially in the beginning of treatment. One to 2 teaspoonfuls of sodium bicarbonate to the quart of water should be used and washing persisted in until the fluid comes away absolutely clear, at the end a pint of distilled water should be run in and out. Depending upon the severity of the case, lavage should be practiced morning and evening, or only in the morning, or only two or three times a week. In Hurst's (1934) experience the use of an ounce (30 cc) of hydrogen peroxide to the pint (500 cc) of water effectively removes mucus and may be followed by the appearance of free acid in the stomach.

Vitamins, Liver, Ventriculin, Iron—Eusterman (1936) stresses the point that one must be sure to provide an adequate intake of vitamins, especially A, the B complex, and C. Schiff and Goodman (1940) induced marked symptomatic improvement and disappearance of atrophic changes in 5 patients given 30 to 60 Gm daily of ventriculin (hog stomach extract).

together with a bland diet, upon withdrawal of ventriculin in 3 patients, 2 showed return of the atrophic changes and 1 an associated return of symptoms. In a fourth patient atrophic changes returned when taking insufficient ventriculin. The results of Schindler *et al* (1940), who used liver and iron therapy instead of ventriculin, do not indicate that such replacement therapy may be expected to be specifically curative in all cases of atrophic gastritis.

Acids and Alkalis—When indicated these agents are used as in hypo- and hyperacidity respectively.

PEPTIC ULCER

(Gastric and Duodenal Ulcer)

Gastric ulcer occurs nearly always at a distance of 2 inches or more from the pylorus, duodenal ulcer is usually located $\frac{1}{2}$ inch or more away from the landmarks which divide the stomach and duodenum, pyloric and primary jejunal ulcers are rare. It is thought that multiple ulceration occurs in between 20 and 30 per cent of cases. Gastric and duodenal ulcers are sufficiently alike in their symptoms and treatment that they may be conveniently discussed under the title "peptic ulcer." Ulcer incidence seems to the clinician to be highest in women between twenty and thirty and in men between thirty and fifty, pathologists (Portis and Jaffe (1937)) raise these figures to thirty and forty, and fifty and sixty, respectively. But there are no absolute age limitations, ulcer may occur in the infant only a few days old or in the centenarian. The vast majority of peptic ulcers occur in the duodenum of white males.

The outstanding and characteristic features of peptic ulcer are (a) that the patient is usually actively engaged in the affairs of life, has a normal appetite and is not undernourished, (b) the history is usually of a chronic gastric disturbance of several years' standing, during which time there have been numerous periods without symptoms, (c) there is epigastric pain and tenderness which is extremely variable but not often excruciating and usually not of a radiating type, (d) this pain bears a definite relationship to food intake, which has been described by Moynihan as follows: "In case of gastric ulcer, the pain which, after an interval, follows the taking of a meal, gradually disappears before the next meal. In cases of duodenal ulcer the pain continues until the next meal, or until food is taken to give ease to a wearisome pain. The rhythm of gastric ulcer is 'food, comfort, pain, comfort', and then again 'food, comfort, pain, comfort', of duodenal ulcer it is 'food, comfort, pain', and then again 'food, comfort, pain', a quadruple rhythm in the former disease, a triple rhythm in the latter." The location of the pain to the right or left of the midline is probably of no significance in differentiating between gastric and duodenal ulcer. Posture has usually a definite effect upon the pain. Not all cases of peptic ulcer are so easy to diagnose as this very brief description would seem to indicate, indeed, there are many patients with such a multiplicity of dyspeptic symptoms that diagnosis is extremely difficult, in others, again, nocturnal epigastric pain may be the only symptom. Thanks to the indefatigable efforts of the late Russell

Carman, who himself suffered the ironic fate of an early death from gastric carcinoma, the x-ray has come to play a prominent part in the diagnosis of peptic ulcer. The various motor meals, designed to test the motor sufficiency of the stomach, also yield valuable information at times. The occult blood test is a valuable diagnostic aid, for occult blood is present at some time in the feces of the great majority of ulcer patients, but Palmer (1939) makes the important differential point that its continued absence speaks strongly for benign ulcer while its continued presence after two or three weeks of treatment strongly suggests carcinoma.

Severe hemorrhage and perforation are the two most feared complications of peptic ulcer. In the exhaustive autopsy studies of Portis and Jaffe (1937) hemorrhage as a cause of death occurred in 18.3 per cent of cases and perforation in 20 per cent. However, these figures only mean that those who died of ulcer died in this way, actually, the total mortality from peptic ulcer is very low—indeed it is now the consensus that a goodly number of peptic ulcers give rise to only very slight and transient symptoms and are therefore never diagnosed at all. The general impression among physicians and surgeons alike that bleeding ulcers do not perforate was not completely confirmed by Winters and Egan's (1939) study of 361 patients with perforation, for bleeding had occurred in 10 per cent of these cases. Studley (1936) probably finds many observers in agreement with him in his contention that if a large loss of weight occurs during the medical treatment of ulcer this also should be counted a major complication, since it greatly increases the hazard of surgical measures which may subsequently become necessary.

In the matter of etiology, practically all students of the disease are agreed that the presence of gastric juice, with its ability to digest devitalized tissue, is of foremost importance since ulcer practically never occurs in the entire absence of acid juice. It is true that Ruffin and Dick (1939) have reported achlorhydria in 5.4 per cent of 419 cases of duodenal ulcer and in 6.7 per cent of 42 cases of gastric ulcer, but Palmer and Netter (1940) have pointed out the fallacy of basing the diagnosis of achlorhydria upon a single histamine test and further state that in their own experience with over 2200 cases of proved peptic ulcer no instance of complete and persistent achlorhydria has ever been encountered, witness also the fact that in Kahn's (1937) review of the records of 840 patients with pernicious anemia, and hence achylia, he found not a single case of peptic ulcer. Palmer, Schlundler and Templeton (1938) have beautifully demonstrated clinically, roentgenologically and gastroscopically that (a) ulcer is a penetrative process beginning in the mucosa and invading the deeper layers of the gastric wall, (b) under favorable conditions healing proceeds rapidly and is so complete that the scar is scarcely visible gastroscopically, (c) failure of the lesion to heal may be due to inadequate following of the treatment regimen or to failure of the stomach to empty properly, (d) delayed gastric emptying in these cases is frequently attributable to organic or physiologic narrowing of the antrum, failure of the pylorus to open or both. As to what it is that permits ulceration to begin in the first place we have still only opinions, which are currently too many and too diverse to justify my listing them here. One fact upon which all observers agree is that the person most prone to develop ulcer is the thin, lantern-jawed, highly strung individual very actively and busily engaged in work, worry, and introspection.

It has been almost universally held in the past that gastric carcinoma may develop from gastric ulcer, but the occurrence must be very infrequent, indeed, Hinton and Trubeck (1937) and Palmer (1939) doubt that the transformation ever takes place

THERAPY

MEDICAL VERSUS SURGICAL TREATMENT

The criteria for recourse to surgery, listed by Arthur Dean Bevan a number of years ago, continue in the main to serve as a safe guide

'If I attempt to put the question of the medical and surgical treatment of ulcer in figures, I should do so in about this way. Almost all ulcers in their early history should be treated medically. When they persist under good medical management, when they recur in spite of good medical management and the care which the patient can obtain in his or her peculiar station of life, when serious and repeated hemorrhages occur, when pyloric obstruction does not yield to good medical management, when there is a reasonable suspicion of malignancy, in all of these cases medical management should not be too long persisted in but should give way to exploration and surgical therapy as the safer plan and the plan which affords the better prospect of cure. Numerically, I believe that these cases demanding surgical treatment for their best interests would constitute about 10 per cent of the ulcers of the chronic type."

It is gastric and not duodenal ulcers which most often pose the problems with regard to choice of procedure, for roentgenologists admit that in 10 per cent or more of gastric ulcers they cannot determine whether the lesion is malignant or not. Walters (1942) says that the clinical symptoms thought to be pathognomonic of benign gastric and duodenal ulcer have occurred in a third of the cases of carcinoma in which operation was performed at the Mayo Clinic, and that in 80 per cent of this group there had been temporary effective response to a medical regimen. In Walter's opinion, therefore, most gastric ulcers should be removed surgically without too much delay

BED REST, FREQUENT FEEDING AND ALKALIS (SIPPY TYPE OF TREATMENT)

The principle of this treatment is to keep the patient in bed for three to four weeks and to maintain what are considered to be ideal conditions for the healing of the ulcer by the use of frequent small feedings and sufficient alkalis to maintain the gastric juice practically neutral in reaction between 7 A.M. and 10.30 P.M. In cases attended during the first few days by copious secretion during the night, this is removed by aspiration two or three times each night until such time as the amount of juice present in the stomach during the night does not exceed 10 cc.

Diet.—In the beginning, 3 ounces (90 cc.) of equal parts milk and cream are given every hour from 7 A.M. to 7 P.M., eggs and cereals being added after two or three days, by the tenth day the patient is receiving, at three of the feedings during each day, one soft egg and 3 ounces (90 Gm.) of cooked cereal. Thereafter, vegetable purées, and other soft and palatable foods, such as cream soups, jellies, marmalades, custards, etc., may be added, but no feeding should exceed 6 ounces (180 Gm. or cc.), and milk, cream, eggs, cereals, and vegetable purées should continue to form the basis of the diet. Lean meat should not be used when it may interfere with tests for occult blood in

stools and aspirated stomach contents It is desirable to have the thin patient gain weight

The Sippy Alkalis—Alkalis are given midway between feedings, alternating the following two mixtures (a) 10 grains (0.6 Gm) each of heavy magnesium oxide and sodium bicarbonate, (b) 10 grains (0.6 Gm) of bismuth subcarbonate or calcium carbonate and 20 to 30 grains (1.2–2 Gm) of sodium bicarbonate

Efficacy—Formerly used almost to the exclusion of all other methods, the Sippy treatment has nowadays been superseded to a considerable extent by the methods subsequently to be described However, Wosika and Emery (1936) reaffirmed its efficacy in a carefully performed study in a group of 55 patients

Simultaneous Administration of Milk and Alkali—The observers just cited above have also been giving powdered milk and alkalis together in one dose at intervals of one hour instead of alternating feedings and dosing with alkali at half hour intervals as in the classical treatment Latterly, Wosika (1938) has reported the substitution of 12.5 Gm of powdered skimmed milk for 90 cc of milk and cream He reduced the amount of sodium bicarbonate from 2 to 0.6 Gm and increased the amount of calcium carbonate from 0.6 Gm to 2 Gm This mixture, given in tablet form once an hour was said to have resulted in a more complete neutralization of gastric acidity than was possible with the routine Sippy procedure

Alkalosis Accompanying the Regimen—According to the accepted standards for an ideal antacid (i.e., that it is insoluble, does not irritate the stomach and intestines, is neutral in aqueous suspension but capable of neutralizing acid, does not unduly alter the acid base equilibrium in the body, when taken in any reasonable amount will not alkalize the urine with the attendant danger of precipitating crystalline phosphates in the kidney or ureter, will not cause diarrhea or constipation, and will not seriously alter the mineral metabolism), sodium bicarbonate is far from satisfactory It is soluble in water, it is irritating in high concentrations, it is absorbed and produces alkalosis when taken in excess, and it alkalizes the urine and occasionally causes the precipitation of crystalline phosphates in the pelvis of the kidney, the ureter or bladder Lockwood and Chamberlin have reported that sodium bicarbonate in about one half the patients examined caused a rebound in gastric acidity to a point higher than would have been attained had the alkali not been administered Also of considerable importance is the fact that numerous observers have reported the development of alkalosis in Sippy treated patients The symptoms of alkalosis most often noted are headache, aversion to food, dry mouth, excessive thirst, lassitude, nausea and sometimes vomiting, in more than usually severe cases mental deviations may appear, together with muscle and joint cramps, dizziness and tingling in the extremities, and spasmodic movements With some patients these symptoms appear soon after beginning the alkalis, with others later on At times they pass away in a few days even though the alkalis are continued in the same amounts indicating perhaps, that the organism makes some sort of compensatory adjustment in these cases Again, the toxic symptoms become so pronounced and persistent that the alkalis have to be stopped for a few days, and sometimes the symptoms return as soon as the alkalis are resumed so that they have to be abandoned at least in quantities sufficient to neutralize

the free hydrochloric acid continuously. In cases with severe vomiting and threatened tetanic convulsions it is necessary, in addition to stopping alkali and food administrations, to give large quantities of physiologic saline solution intravenously to compensate for the chloride losses. Kirsner and Palmer (1941), in 27 patients developing alkalosis on calcium carbonate alone, were able to continue administration of the alkali and overcome the alkalosis by simply giving in addition 5 to 15 Gm. of sodium chloride daily. This is a very rational procedure because chlorides are lost from the system in any type of alkalosis even though there is not vomiting. Rafsky *et al.* (1932) reported a successful attempt, in 61 cases with adequate controls, to build up a tolerance for alkalis, as follows: daily doses of 50 grains (3.3 Gm.) sodium bicarbonate, 20 grains (1.3 Gm.) calcium carbonate and 12 grains (0.8 Gm.) magnesium oxide, gradually increased by the end of the second week to 160 grains (10.0 Gm.), 35 grains (2.3 Gm.) and from 12 to 20 grains (0.8-1.3 Gm.), respectively. In absence of clinical or biochemical evidence of alkalosis, the dosage was further increased until there was a complete cessation of symptoms, for which the average maximum dose necessary was 315 grains (21 Gm.) sodium bicarbonate, 60 grains (4 Gm.) calcium carbonate and from 12 to 35 grains (0.8-2.3 Gm.) magnesium oxide.

There have been numerous references to renal damage in alkalosis resulting from the use of alkalis in peptic ulcer. Eisele (1939) feels that the work of the kidneys is greatly increased; he found the urinary excretion of solids nearly doubled. The nitrogenous elements, as well as inorganic phosphates and sulfates, may rise in the blood. Kirsner and Palmer (1941) find it unusual, however, for albumin casts and red blood cells to appear in the urine. With regard to the association of alkali therapy and stone, the evidence is conflicting. Kretschmer and Brown (1939) found that the small incidence of patients who had been treated for ulcer among their 1260 cases of kidney and ureteral stone was not of statistical significance, while Eisele (1940) found the incidence rather high among his 505 cases.

Vitamins—Archer and Graham (1936), Bourne (1938) and Portnoy and Wilkinson (1938) have found patients on ulcer diets often in the subclinical stage of scurvy, which suggests of course the advisability of using adequate amounts of ascorbic acid (vitamin C). Latterly there has been interest also in supplying other vitamins in these cases (see chapter on the Deficiency Diseases for methods).

Substitutes for the Sippy Alkalis—The neutral antacids, tricalcium phosphate and trimagnesium phosphate, have been tried, usually together in doses of 10 to 20 grains (0.6-1.5 Gm.) each. They do not often adequately serve to neutralize the amount of acid present. Mutch (1936) in England introduced synthetic hydrated magnesium trisilicate, which has since been satisfactorily used in a dosage of 15 to 30 grains (1 to 2 Gm.), occasionally as high as 60 grains (4 Gm.), by a few men in small series of cases with apparent satisfaction, one advantage claimed for this agent (Mutch, 1937) is that it will not cause alkalosis. Heffner *et al.* (1941) have found small amounts of silica excreted in the urine but no evidence of toxicity therefrom.

Kirsner and Palmer (1941) have been comparing antacids in peptic ulcer patients with a technic comprising hourly removal of gastric contents for determination of relative acidity and hourly administration of the alkali. The drugs studied have been calcium carbonate, sodium bicarbonate, alumi-

num hydroxide, tricalate, tribasic calcium phosphate, magnesium trisilicate, magnesium carbonate, and tribasic magnesium phosphate. In their first report they stated that calcium carbonate (one of the Sippy alkalis), in doses of 2 to 4 Gm., is the most effective neutralizer of gastric acidity, subsequently they have said that magnesium carbonate (not yet tried at the time of the first report) is also highly effective in 2 Gm. doses.

Steigmann and Fantus (1940) found that a number of 'antacids' give symptomatic relief without producing a uniform and constant reduction in gastric acidity, from which they concluded that the relief of pain is secured in a different manner than simply by means of antacid action.

Atropine.—Kirsner and Palmer (1940) report that atropine sulfate, given orally in four $\frac{1}{16}$ -grain (1 mg.) doses daily, did not affect the reaction of the gastric contents though it did apparently reduce the volume of the secretion. They find it very helpful when used as above in addition to alkali therapy, the result in their opinion being due to atropine's prolongation of gastric emptying time as well as its reduction of the volume of gastric secretion.

AMBULATORY WITH FREQUENT FEEDINGS (ALVAREZ TYPE OF TREATMENT)

While admitting that the Sippy treatment is often effective, Alvarez has the following objections to make: (a) it requires more training, enthusiasm and faith in this particular type of treatment than can be expected from the average busy practitioner, (b) it requires an expensive month in hospital, (c) only a very few patients can be expected to come back to the hospital for subsequent Sippy treatments for each recurrence, (d) the lack of evidence that the period of relief after a Sippy cure is longer than after little or no treatment, (e) the observation that frequent feeding is perhaps the most valuable item in the cure, (f) and the fact that, 'whether the profession likes it or not,' most patients with ulcer will continue to try to worry through their attacks and keep at their work. In view of these considerations, Alvarez champions a simple form of ambulant frequent feeding treatment that has the best prospect of being practicable for the average physician and the average patient.

Diet.—The patient is given three good meals daily and the attempt is made to fatten him if, as is usually the case, he is underweight. The only stipulation is that foods which contain scratchy material such as raw fruit, bran, many of the green vegetables unless pureed, celery, salads, nuts, gristle, and berries, are to be excluded (see the "smooth diet" list under Nervous Indigestion). Alvarez is not certain that such care is important, but since many patients experience no great privation with this amount of restriction, he feels that "smooth" dieting should be instituted in most cases. Meat is not forbidden. Windwer and Matzner (1939) have in fact proposed that in addition to the use of lean boiled meat, chicken, cottage cheese and milk, the patient take about 8 Gm. of unflavored gelatin in a quarter glass of water at hourly intervals between feedings for seven doses daily. In justification of this high protein diet these authors allege the following: (a) Proteins can neutralize acids by their acid binding properties. (b) Peptic activity may be inhibited by the "competitive retardation" of the products of digestion of proteins. (c) The ample supply of amino acids will restore a deficiency believed by some to be a causative factor in the production of ulcer.

The important part of the treatment consists in the taking of food between meals. The mixture used consists of a quart of milk, two eggs and from 1 gill to $\frac{1}{2}$ pint of cream. Of this a glassful is drunk at 10 A.M. and another at 2, 4, 8 and 10 P.M., with an additional one during the night when awake. The patient intolerant of milk may use a thin gruel made from any cereal. In some patients pain will recur within one and one-half hours, in which case the feedings must be taken every hour and fifteen minutes—but Alvarez finds that these individuals usually do not do well on medical treatment. However, Dick and Eisele (1942) have recently described their satisfactory treatment of a series of 41 patients with 1 to 4 ounces (30 to 120 cc.) of a mixture of equal parts of milk and cream at hourly intervals during the day and often during the early evening, using milk alone in a few instances in which cream was poorly tolerated.

Vitamins—See under Sippy treatment on a preceding page.

Alkalis—Not routinely used in this type of treatment.

Exercise—The patient is to rest as much as possible on Saturdays and Sundays. Walking is about the only exercise that is allowable at any time, golf, gardening, and any bodily movements that are likely to cause pulling on the duodenum, are to be given up. "One must remember that the first portion of the duodenum serves as a sort of hook from which the stomach swings like a hammock, and I believe that this anatomic arrangement has something to do with the tendency toward ulceration at that point. Men often say that it is the hard work in spring or fall, plowing or pitching hay, which brings their recurrences, and I have seen a number of cases in which, even after operation, the patient could stay well only by avoiding lifting and bending. In fact many persons can obtain permanent relief only by changing to a sedentary occupation."

Duration of Treatment—Most patients are quickly made comfortable on this regimen but they must nevertheless persist in it for six months or preferably a year. Many will remain free from discomfort thereafter only if they abstain from exercise and take small bits of food in the middle of the morning once or twice in the afternoon, and perhaps again before retiring. Alvarez says that many of them grow tired of being semi-invalids even to this extent and sooner or later ask for operation.

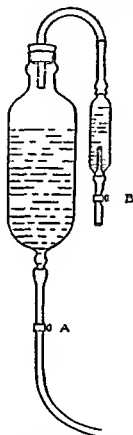
ALUMINUM HYDROXIDE

The French custom of using aluminum hydroxide as an antacid devoid of deleterious effects was introduced into America by Crohn in 1920, but it is the more recent work of Einsel and Woldman and their respective associates that has established it in its present place of high esteem in this country.

This method of treating peptic ulcer resembles the classical Sippy method in that very ill patients are kept in bed on frequent feedings of a bland diet, it resembles the Alvarez method in that less severely ill patients are maintained in an ambulatory state with quite similar frequent feedings. But it differs from these methods of treatment in that it substitutes for the alkalis of the Sippy regimen, and the lack of alkalis of the Alvarez regimen, the frequent administration of the acid neutralizing substance colloidal aluminum hydroxide. This substance has a high acid-combining power and a desirable degree of astringency and it coats the ulcer surface with a protective jelly like mass. Unlike the carbonates it does not liberate large quantities of carbon

dioxide and it is not laxative, like the magnesium salts, furthermore it does not induce compensatory acid secretion as does sodium bicarbonate. A further very great advantage of the agent is that it is not absorbed and hence does not disturb the acid base balance, *i e*, it does not cause alkalosis. There are now available many highly favorable reports of this method of treatment all

FLASK FOR DRIPPING ALUMINUM HYDROXIDE
(After Woldman and Rowland)



Technic.—1 Fill the Kelly (larger) flask to the top with a 1 per cent suspension of colloidal aluminum hydroxide while clamp (A) is closed. 2 Fill the inverted Murphy drip tube with water while clamp (B) is closed. 3 Insert the rubber stopper securely into the mouth of the Kelly flask and connect the inverted Murphy drip tube to the short rubber tube with screw clip as indicated in the diagram. 4 Attach Kelly flask to a hook or standard so 3 feet above the level of the patient's stomach. 5 Open clamp (A) wide. 6 Open clamp (B) just enough to allow air to bubble slowly through the water in the Murphy drip tube (about fifteen bubbles a minute). 7 After the rate of flow is established and the nasogastric tube is comfortably in position attach the outflow tube to the nasogastric tube by a glass connection.

agreeing that pain is rapidly relieved (usually, indeed within twenty four hours) healing rapidly accomplished (*i e*, niches frequently disappearing in seven to ten days and larger craters filling in two weeks), results often obtained with this treatment in patients in whom other methods have failed and an incidence of recurrences certainly no greater than with other methods.

Drip Administration—This method requires hospitalization but it is the preferred method to accomplish rapid healing and also the necessary method in very ill patients. The colloidal aluminum hydroxide preparation is continuously instilled into the stomach through a nasogastric tube at the rate of 15 drops per minute, day and night, for ten days in average cases. The earlier troubles from clogging of an ordinary Levin tube and complaints when a larger Levin tube was used have now been overcome by the substitution of a soft collapsible thin rubber tube about $\frac{1}{4}$ inch in diameter. This tube is passed through the nose into the stomach with the aid of a silkworm gut suture which acts as obturator and is left in place within the tube to prevent its kinking. The tube is passed only as far as the end of the esophagus. The older three flask method of delivering the solution has now been replaced by the one flask method of Woldman and Rowland (1941) depicted and described herewith.

Since the astringent action of aluminum hydroxide tends to cause constipation mineral oil is usually given daily, or an enema every other day.

Oral Administration—When patients object to or cannot tolerate the tube, the drug may be given by mouth in an average dose of 1 to 2 drachms (4 to 8 Gm.) stirred up in a little water at intervals of one hour during the day and every two hours during the period of sleeping, giving a sedative in the evening so the patient will go quickly back to sleep when roused through out the night.

Ambulatory Routine—In the experience of Collins *et al.* (1941), treating 154 patients who carried on in their usual occupations the following routine was satisfactory, though of course it had to be modified according to severity of symptoms: (a) a dose of aluminum hydroxide every two hours during waking hours for the first three months, either a meal or a glassful of milk being taken midway between the doses, (b) during the next three months, a glassful of milk midway between meals and a dose of the drug one hour after each meal, after each glassful of milk and at bedtime, (c) during the remainder of the first year's treatment the taking of the drug after the three main meals and at bedtime.

MISCELLANEOUS TYPES OF THERAPY

The following methods of approach no longer seem to me to merit space for their description: physiologic rest through venoclysis (Hendon type of treatment), milkless diet with white of egg and butter (Jarotzky type of treatment), continuous alkalinized milk drip (Winkelstein type of treatment), muen treatment, histidine treatment.

Metz and Laehey (1940) report good results following the employment of powdered posterior pituitary preparation as in diabetes insipidus but their work remains unconfirmed. In 1938, Bergh reported that the oral administration of bile salts was helpful in a large proportion of a small series of cases but in the same year the independent findings of Emery and Sebnitker were not nearly so favorable.

TREATMENT OF HEMORRHAGE

The indications here are to combat shock, combat dehydration, prevent digestion of the edges of the exposed blood vessel, promote clot formation, restore the blood volume and maintain nourishment. In some instances resort to surgery is necessary.

Shock—Morphine (or dilaudid) should be given hypodermically in practically all cases not only because of its influence in quieting the patient physically, but because it greatly reduces fear, which is a contributing factor of great importance in shock, the later "splinting" effect upon the bowel is unfortunate but cannot be helped. If, as occasionally happens, it does not reduce the restlessness or causes severe nausea, a barbiturate may be given hypodermically (pentobarbital sodium, 3 grams [0.2 Gm], phenobarbital sodium, 2 grains [0.12 Gm], amytal sodium, 3 grams [0.2 Gm], barbital sodium, 5 grams [0.3 Gm]), or chloral hydrate, 20 grains (1.2 Gm) in a little water, may be introduced into the rectum.

Dehydration—This condition is combated by proctoclysis or hypodermoclysis with saline or Locke's solution, or by the intravenous administration of dextrose. It has not been proved that rectal administration of fluid stimulates gastric motor activity. These fluids only counteract dehydration, *i e*, they do not restore blood volume. Many men feel that the addition of 6 per cent acacia is of value, but the point is not established. Hunter (1936), who has been accused of preferring this measure to blood transfusion, has made it perfectly clear that he thinks it only a stop gap while preparations for transfusion are being made. A frequent practice is to elevate the foot of the bed to "help the cerebral circulation", Wood (1936) has well pointed out that venous return from the head may be so much impeded in this way as to contribute to the stupor by promoting cerebral edema.

Protect the Bleeding Area—A good many years ago Rodman advocated immediate lavage with the ordinary stomach tube and water somewhat above body temperature. The measure, designed to rid the stomach of clot which acts as a stimulant, has not remained popular, but Smithies (1935) considered it indicated if there is much vomiting and retching. Under the latter circumstances, Bolton (1936) prefers to attempt to dilate the pylorus with atropine atropine sulfate, $\frac{1}{16}$ to $\frac{1}{8}$ grain (0.0006-0.0012 Gm) hypodermically, or tincture of belladonna, 20 to 30 minims (1.2-2 cc) by rectum, the doses to be repeated twice daily if necessary. In recent years, Soper has proposed continuous lavage: the nasal mucosa is shrunk with 2 per cent cocaine hydrochloride, a Levin tube with a tip finished like that of the ordinary soft rubber catheter is passed by that route—slowly to prevent coiling, the patient swallowing water with each advance of the tube—siphonage to a bottle is established, and the stomach thus kept cleaned out. It is felt that the raw surface is protected from corroding gastric juice by this method, and that nausea and vomiting are prevented and the patient kept remarkably comfortable. The hemostatic agents are injected through the tube, and egg albumin and gelatin water given by the same route. On the third to fifth day the tube is passed on down into the intestine, intravenous injections of dextrose are discontinued, and a high calorie mixture of raw eggs, milk, cream and lactose is fed through the tube. This method provoked adverse criticism when it was introduced in 1931, but Soper pointed out that no one criticized who had used the tube, in 1936, he (Thompson and Soper) reiterated his confidence in the method.

Promote Clot Formation—Quiet, of both body and stomach, is of course the chief measure here. The application of an ice-bag to the epigastrium is thought by many practitioners to be of value, to me it seems that it can be of aid only in helping to hold the patient motionless. Smithies (1935) and

Andresen (1939), pertinently pointing out that such a measure only further chills a patient already in shock, prefer the opposite and more rational measure of keeping the patient warm

Calcium thromboplastin or none of the other alleged hemostatic agents have proved to be of any worth

Woldman (1941) has used his aluminum hydroxide treatment (described earlier in this article) with apparently excellent results in 144 patients in 86 by the drip method, in 42 by the mouth only, and in 16 by a combination of the two methods. He contrasts the mortality rate of 2 per cent in this group with the rate of 28 per cent in the same hospital during the 5 years preceding inauguration of aluminum hydroxide therapy. It is alleged that this agent promotes clot formation and then protects the deheated fibrin from the action of strong unbuffered gastric juice

Restore Blood Volume—It is now almost unanimously agreed that transfusion of blood for the restoration of blood volume is indicated in all but the lightest cases of hemorrhage, among those who oppose what they consider the too frequent resort to this measure are some potent voices however, perhaps most notably Hurst and Ryle (1937) in England. In the United States Crohn and Lerner (1939) are also not to be described as enthusiastic supporters of this measure, they feel that transfusions should be used sparingly and in small amounts preferably after the blood pressure has stabilized and when the symptoms of shock have subsided—threatened death due to anoxemia is the only immediate indication which they recognize. Nevertheless the continuous drip method of transfusion, introduced by Marriott and Kekwick (1935) is apparently winning an increasing number of advocates. Cubitt (1937), Gordon Taylor (1937), Jones (1939), etc. But Crohn and Lerner are apparently opposed to even this measure in most instances because, while admittedly it does not cause any considerable rise in blood pressure the excitement incident to the procedure may sufficiently disturb the patient as to induce recurrent bleeding. MacGuire (1935) favored massive transfusions—as much as 1000 cc., perhaps repeated three times in one of Crohn and Lerner's cases in which 1200 cc. had been given inadvertently the whole amount was shortly given back in one large hematemeses.

Black and Smith (1941) found that plasma transfusions affected their patients adversely.

Diet.—The vast majority of the profession is in favor of keeping all food out of the stomach for several days employing dextrose intravenously either intermittently or by venoclysis or feeding by rectum. It must be admitted that not much nutriment can be introduced by the latter route since we are limited to the giving of dextrose peptones and alcohol. The following is a typical formula the whole of this mixture being introduced into the rectum by the drip method three or more times in twenty four hours

R. Wele's peptone	5j	30 0
Alcohol	5ss	15 0
Glucose syrup	5j	50 0
Saline solution to make	5viij	150 0

When mouth feeding is resumed (generally about two days after a rising blood pressure slowing pulse with improved quality and an improving blood picture indicate cessation of bleeding) it is usual to begin with frequent feed

ings of barley gruel and fruit juices, adding custards, strained soups and pureed vegetables gradually, and allowing meats which tend to increase acid secretion only much later

In contrast to the above position, Andresen has been maintaining that an empty stomach is never at rest and that it should be kept at least partially filled from the beginning with food that combines readily with gastric juice and does not overstimulate its production. He uses a liquid mixture of gelatin, 30 Gm, dextrose 60 Gm, cream (20 per cent), 100 cc, milk, 600 cc, the formula to be made fresh every twelve hours and kept cool but not placed in the refrigerator in order to avoid jelling. For the first four days, the patient receives 6 ounces of this mixture (chocolate vanilla coffee or tea flavored if desired) every two hours. On the fifth and sixth days any one of the following is added to 4 of the feedings:

1 egg—soft boiled, poached or raw
Cereal—3 ounces
Custard, jello or ice cream

On the seventh and eighth days two of the above foods are added to each of 3 feedings, and on the ninth day the patient goes back on to regular ulcer diet. If at the beginning of the above-outlined regimen the patient cannot tolerate the thick gelatin milk mixture he is given for awhile the following formula: gelatin, 30 Gm, dextrose, 60 Gm, juice of 2 oranges, water 1000 cc. Andreesen has been employing this treatment at the Long Island College Hospital since 1916. LaDue (1930) finds that the mortality rate has been only 1.3 per cent.

The similar full feeding regimen of Meulengracht in Denmark, adopted apparently sometime after Andreesen's first publication, has caught the medical fancy more fully here in America, probably because it was originated further away. In the most recent of Meulengracht's (1939) publications to come to my attention the diet is still the same as described in the first paper which appeared in 1933:

6 A.M.—Tea, white bread and butter
9 A.M.—Oatmeal with milk, white bread and butter
1 P.M.—Dinner of any soft nourishing foods in unrestricted amounts: meat balls, timbals, broiled chops, omelette, fish balls, vegetable meat or fish au gratin, mashed potatoes, pureed vegetables, vegetable soup, creamed vegetables, stewed apricots, apple sauce, gruel and rice and tapioca puddings
3 P.M.—Cocoa
6 P.M.—White bread and butter, slices of meat, cheese and tea

Meulengracht's results are about like those of Andresen, there are a number of recent reports of equal satisfaction with this diet. Herlitz (1938), Boyd and Schlachman (1938)—with some reservations, Mayer and Lightbody (1939), Chasnoff *et al* (1940), Miller (1941). Crohn and Lerner, in 1939, were holding out against the treatment. Rafsky and Weingarten (1942), in a recent appraisal of various methods of treatment, were able to follow the Meulengracht plan without interruption in 26 of the 39 patients in whom it was tried, discontinuance was due to the following factors: recurrence of bleeding in 7 patients, 3 of whom died, severe pain in 3, 1 of whom had a perforation of his ulcer and died postoperatively, and severe nausea and vomiting in 3.

Resort to Surgery—Surgical statistics are not in complete agreement regarding indications for intervention, which likely means that medical and surgical judgment must still weigh each case separately. However, I believe that all observers, even those surgeons who hold that Finsterer's "first forty eight hours" is still the optimum period for surgical attack in the bleeding of chronic peptic ulcer, will agree with Lynns and Brenner (1939) "It appears that young individuals with bleeding ulcers rarely die, and when they do it is usually as a result of complications rather than exsanguination. It also seems that in this series death from exsanguination was not as a rule sudden, even in old people, but occurred only after several days of continued bleeding."

TREATMENT OF PERFORATION

Acute perforation demands immediate surgical intervention. Most patients recover who are operated upon within six hours after the perforation has occurred, for each hour after that time the chances of death are greatly increased.

COLON CONSCIOUSNESS

(Constipation, Mucous Colitis, Unstable Colon, Visceropsosis)

This condition can no longer be satisfactorily presented as comprising several distinct entities each resting upon its separate pathologic basis for the unity of the functional disorder underlying them all has now been firmly established. It is primarily a disturbance of the conditioned reflex upon which normal defecation depends, characterized by changes in colonic tone, irritability and secretory activity, induced by environmental imbalance in a neuropathic individual, aggravated by "treatment," and expressed as awareness of the colon and its activities. The normal physiologic behavior of the colon and rectum is quite simple. When a meal is taken the ileocecal valve is relaxed and the contents of the ileum are propelled by peristaltic action into the cecum and ascending colon. Simultaneously, waves of contraction sweep along the colon to convey the contents into the pelvic portion, haustrations (segmental movements) at the same time serving to effect intimate contact with large surfaces of the mucosa so that water is absorbed and the feces converted into their final form. In the infant there is no mental control of the terminal stage of this stuffing process, a lack with results that are well known. But in the course of time—I am following Hurst closely at this point—an elaborate conditioned reflex develops in which getting up in the morning, a bath, dressing, breakfast, and finally sitting down in the familiar w.c. take part, with the result that the biggest colonic peristaltic wave of the twenty-four hours takes place, the rectum is filled, there is the "call to defecate," the diaphragm and abdominal wall are voluntarily contracted and contraction of the rectum with relaxation of the anal sphincter permits the feces to be evacuated. In most adults this scene is enacted diurnally, but not in all, for there are many individuals who skip one or several days and are not in the least disturbed provided their absorption with life is properly

extroverted The colon-conscious fellow is troubled, though! For not only does he come complaining of the number of days he has failed to have an evacuation, but he knows that the stools, when they do oblige him, are ribbon like, pencil shaped, accompanied by much mucus, and so on, and he clamors for the opportunity to tell about these things to assist the doctor, whose mind's eye is of course ever steadily fixed on the standard stool encased with the meter bar in Paris. More often than not he is also wedded to the fascinating idea of "auto intoxication," about which faddists (not all outside the profession) and the daily newspapers hold forth with unremitting gusto, so that many times the stool he tells about is really only dimly remembered, since for months or years he has kept himself satisfyingly musby or even in a state of chronic diarrhea with drugs. Or the bowel is washed out with enemas or irrigations, at home or in commercial establishments which exist for the purpose. The abdomen is of course often tender in colon-conscious patients and the descending colon may be palpable as a tender cordlike structure, sometimes there are paroxysms of severe abdominal colic. "Viscer optosis" is a term which has caught on well with these patients, though scientific proof is still lacking that a cecum offends heinously by mere residence in the pelvis. Not all of those who know of their affliction escape the surgeons, and those who do are almost certain to control themselves by day with monstrous hinders and by night with prodigious exercises in the bed, the latter usually culminating, I believe, with a slide down onto the abdomen from the knee-chest position so that everything will remain safely tucked up during the long dangerous night.

THERAPY

In an ancient recipe for rabbit stew one is enjoined to "first catch your rabbit." How sound that advice is when applied to the subject in hand, first be sure that the patient before you is suffering from simple colon consciousness before you undertake to treat him. Gynecologic, proctoscopic, sigmoidoscopic, roentgenologic, internologic (if I may coin the word) examinations may reveal many primary or secondary organic causes for the syndrome: adhesions, pressure of other organs or of new growths upon the bowel, reflexes from eyestrain, early pulmonary tuberculosis or thyrotoxicosis, chronic appendicitis, gallbladder disease, inflammation of the female adnexa, or of the stomach, liver or pancreas, etc. There are many resemblances between allergic states and the condition of being colon conscious, especially in those instances in which the symptoms are of intermittent and spasmodic nature. Should it be possible to determine the offending substance and to eliminate it from the diet, or environment, or even to desensitize the patient to it, much misery will be avoided and a near miracle performed. The matter does not find such simple allergic solution nearly so often as could be desired, still any case may always be the lucky one. In summary then, the patient must be given the benefit of thorough examinations of all sorts, and only if these are convincingly negative is he to be assigned to the group under present consideration.

Psychotherapy—Read the brief presentation of Alvarez' psychotherapeutic approach to the patient with nervous indigestion (see Index). Indeed, there seems to be little difference between patients suffering from one or more forms of "indigestion" and those bothered by awareness of the colon.

and its performances, save that the latter center their disturbances lower in the tract. All of these individuals need readjustment to something in themselves or in their environment. It is the practitioner's duty to find that something, then to lead the patient to face and live with it. I know nothing easier to set down in a few words!

Habit and Defecation Posture—The stool should be visited by every person every morning after breakfast. Too often housewives who are busy at this time, and men who take their breakfast at a quick lunch counter en route to the office, "put it off" until the desire is no longer felt. After the conditioned reflex has become dulled through such disregard and "constipation" has set in, if one impresses the necessity of the regular daily visit upon these people they often accept the advice and carry it out with a grim determination which easily defeats their purpose, for defecation is accomplished only by the maintenance of a nice balance between contraction and relaxation. A few puffs of a cigaret, a few peeps at a newspaper or magazine, is a recipe well known to many persons. Sometimes placing the feet upon the round of a chair so that the thighs are flexed on the abdomen is helpful, the principle is anatomically, physiologically, and traditionally sound—surely the early morning sun the world around still catches the majority of mankind squatting upon its heels at this daily duty. In infants one must also reckon at times with lack of ability or desire to use the expulsive forces necessary for defecation.

Exercise—Bodily exercise is of value in the promotion of general well being, and if it can be taken in the form of some competitive game in which the maladjusted hypochondriacal patient will lose himself for awhile, may be counted upon to be of considerable assistance in the treatment of these cases. But in and of itself it probably has little value, even letter carriers, who could never be rightly accused of a sedentary existence, are said to be a constipated lot. Massage of the abdominal muscles, or rolling a heavy ball about over the abdomen, is nowadays frowned upon because of the danger of doing injury to deep structures by abuse of these measures.

Diet, Bran, Agar, Psyllium, and Beet Pulp—Present belief is that the colon of the patient suffering from functional disturbance of the organ is practically always in a spastic state due to hyperirritability, and that the best thing to do for such a colon is to give it rest by the use of a smooth diet (see Nervous Indigestion). The rational thing is to take the patient off his beloved cathartics and enemas and wait to see what happens after a while on a smooth diet, in some instances it will be necessary to use more raw fruits and green vegetables than that diet provides, in others not, but there is no way to predict this until the colon has been allowed to fill after the punishment ceases. The old division of constipation into two types, spastic and atonic, has fallen down under more careful study, and with it has gone the conception that the chief trouble in the atonic variety was that the patient ate too little roughage and therefore needed to gorge himself on such things as lettuce, celery, endive, spinach, carrots, beets, string beans, figs, dates, raisins, and prunes. It is true, as already said above, that some individuals seem to need more bulk in the bowel than others and the above foods provide this nicely, but such individuals are certainly in the minority and there is now believed to be little justification for excessive roughage feeding of every person in whom roentgen study after a barium meal or

enema shows evidences of decreased colonic tone. An occasional patient will get a nice effect from a small amount of bran in the form of cookies, muffins, bread cakes etc or taken with sugar and cream to replace the morning cereal but leading gastro-enterologists are now firmly opposed to its use in most cases since it robs any diet of whatever property of 'smoothness' it may have had. Certainly all individuals should be warned against using bran on the principle that if a little is good a lot is better. It is not surprising that there are on record one or two instances in which silly individuals have actually stuffed the gut with this dry material until they produced obstruction. Olmsted *et al* (1936) have used 1 to 2 tablespoonfuls of beet pulp with satisfaction in a small series of cases. Some observers have found that bulk can be satisfactorily provided without irritation through the use of 1 or 2 tablespoonfuls of ordinary x ray barium taken in water two or three times daily. Some colon-conscious patients are made worse not only by the physical irritation of roughages but also by the fact that they suffer from excessive intestinal fermentation (see Index) and they therefore react to these cellulose materials by the production of large amounts of gas. Agar passes through the intestinal tract without undergoing bacterial digestion and merely softens and adds bulk to the feces by virtue of its property of retaining water. It is best used in the form of shreds or a coarse powder, for when finely pulverized it too may produce colic, according to Fantus. It is usually employed in several tablespoonful doses incorporated with foods at the table. Psyllium is a small brown seed that exudes a considerable amount of mucilaginous material when it is moistened. The dose is 2 to 4 teaspoonfuls stirred up with twice as much hot or cold water until a gelatinous mass is formed, which is then spread on bread or taken with cream and sugar, with stewed fruit, or in soup, some people like to place the seed in fruit juice and drink the mixture with mastication, a mixture of psyllium and agar is commercially available. Thienes and Hall (1941) found that psyllium caused pigmentation of the kidneys in experimental animals, but that neither in these animals nor in 9 patients who were long time users of the agent did it cause any evidences of damage to renal function. Karaya gum, which absorbs and holds a large quantity of water in the tract, is the newest of the agents of this type which exert their effect by physical rather than chemical action, it seems to cause intestinal irritation in some instances and Alvarez (1940) has reported a case in which migrainous attacks were attributable to the use of this agent.

The Enema—Ordinarily one of the chief indications is to break a vicious enema habit, which can best be accomplished by sharply forbidding further resort to the measure, still, this is an ideal which, as in all the affairs of man, can often be only approximately realized or must at least be approached through a series of compromises. When it is felt that an occasional enema must be allowed during the time that one is waiting for sound psychotherapy plus cessation of routine dosing, to bring about normal evacuation, it is well to bear in mind that a pint of cool water containing a teaspoonful of sodium chloride or sodium bicarbonate is to be preferred to the ordinary soap suds enema, which is so irritating to even the normal bowel that for some time after its use the mucous membrane presents an angry red appearance. Perhaps it is more rational to inject a small amount of oil at night as a retention enema about 8 ounces (90 cc.) of cotton seed oil or liquid

petrolatum, warmed, olive oil is likely to be irritating. The older custom of injecting large quantities of oil upon retiring, and to make an elaborate ritual of the procedure, is no longer in favor. If the feces have already become impacted, the reader should bear in mind that the injection of water, not oil, is indicated. When use of an irritant is actually required, Levy employs a mixture of 5 cc. of rectified oil of turpentine, 25 cc. of cotton seed oil, 45 cc. of glycerin, and 45 cc. of soft soap. One to 2 teaspoonfuls of this mixture are added to 4 ounces (120 cc.) of water and injected into the rectum by means of a rubber bulb syringe. The action is quick and complete only because this concoction is violently irritating.

Suppositories—Graham pointed out some years ago that if rapid evacuation of the rectum and colon is desired, a 5 grain (0.3 Gm.) quinine dihydrochloride suppository will promptly produce a large but not watery stool. Glycerin suppositories have of course been in use since time out of mind.

Colonic Irrigation—Bastedo is perhaps the principal champion in this country of the use of colon irrigations in so-called "mucous colitis", Friedenwald and Morrison and a few others, favor the method also. But the vast majority of those who confine their practice largely to gastro-enterology flay the procedure as being based upon an entirely erroneous conception of the nature of mucus secretion in the bowel. Hurst points out that the mucous membrane of the colon, like all other mucosae, secretes mucus as a response to both mechanical and chemical irritation as a sign of healthy activity. The passage of dry hard feces is often thus facilitated. When a purgative is taken, the irritation likewise induces considerable secretion, and rapid passage permits much mucus to appear in the loose stool. An enema, especially one containing an irritant, will do the same thing. It is true that the long colonic irrigation will oftentimes bring away masses of mucus, but I think that one of Hurst's case reports with his comments thereon, offers an illuminating explanation for the phenomenon. "A boy of 18 had always had a tendency to constipation and had been continually dosed by his mother with aperients. His report stated that he had been given an irrigation of 30 pints, the treatment lasting one hour and ten minutes. 'The first 12 pints brought away loose faeces but no mucus, but after that a large quantity of jelly mucus was passed continuously until the end of the treatment.' That is to say, 12 pints of fluid were required to irritate the healthy mucous membrane of this boy sufficiently to produce excess of mucus, but when once it began to be secreted it naturally continued, and there would still have been mucus present if he had received 100 instead of 30 pints."

"The patient is often told that the mucus has been accumulating in his colon for weeks or months and that is why he has never seen it in his stools, whereas the truth is that his mucous membrane is none the worse for a few pints of water, but after the first few pints it has to protect itself by secreting mucus. It is sometimes reported that by the end of the patient's 'cure' little or no mucus is present, the explanation being that the patient's mucous membrane responds at first by the secretion of mucus to the unaccustomed irritation, but after some weeks the mucus secreting cells become exhausted and go on strike." Soper maintains that if irrigation is continued long enough, the "foul smelling material" described by Bastedo can be secured in persons having a normal colon, being in his opinion the normal

contents of the ileum changed by the treatment. Krusen reviewed this subject for the Council on Physical Therapy of the American Medical Association, in 1936, it is difficult to find anything very commendatory in his report.

Bastedo's Technic—The irrigation is given from a height of 2 feet using either a No. 34 French tube, velvet-eyed with a closed end inserted about 6 inches, and used for both inflow and outflow of the fluid after the colon has been filled to capacity, or employing the two-tube method in which a 20 to 24 French soft rubber velvet-eyed catheter is inserted 6 inches for inflow, and a 30 or 32 French velvet-eyed closed-end rectal tube (or stomach tube) inserted 3 or 4 inches for outflow. The tubes are inserted about fifteen minutes after an evacuation enema of plain water has cleared the rectum and lessened the chances of disturbances from defecation reflexes. Plain water, slightly above body temperature is used usually 6 to 10 gallons in the course of an hour, the first gallon with the patient on the left side with knees drawn up in order to clean out the lower colon then for the remainder of the time on the back in order for the fluid to reach the cecum. Saline would make the patient very thirsty, and it is doubtful if the vaunted ability of sodium bicarbonate to dissolve mucus outweighs the disadvantages of its stimulation of the kidneys, disturbance of acid base balance and tendency to cause gas and colic. These irrigations are usually employed every day or two for a week, then every three or four days for several weeks longer, and then once a week for as long as considered necessary.

Cathartics—The following drugs are discussed because I have not as yet the courage to omit them, but I sincerely hope that the reader is convinced from the matter presented in the immediately preceding pages that until he weans his patient away from their use he will not relieve the syndrome of colon consciousness.

Cascara Sagrada—This drug is a mild yet reliable cathartic, though one occasionally finds a patient in whom it fails to act. When there is complaint of griping investigation usually discloses that it is being taken in overdose. The ideal dose is one that will produce a single formed but slightly soft stool in the morning when it has been taken on retiring the previous night. The dose of the aromatic fluidextract necessary to accomplish this is from 1 to 3 drachms (4–12 cc), taken before meals and at bedtime or all in one dose at bedtime. The following prescription, in which there are 20 minims (1.2 cc) of the aromatic fluidextract in the teaspoonful offers cascara in a pleasant vehicle, the tincture of nuxvomica so often given with cascara is omitted here because I believe its inclusion to be irrational and dangerous from the standpoint of the poisoning of young children getting hold of such bottles.

R. Aromatic fluidextract cascara sagrada	3x	40 0
Syrup cinnamon	5x	40 0
Water to make	3iv	120 0

Label 1 teaspoonful one-half hour before meals and upon retiring

This dose may be doubled or trebled if necessary but it should be borne in mind that with cascara it is sometimes possible after a while to reduce the dosage gradually without losing effect. Fantus offered the following dosage of the aromatic fluidextract for children

Child 6 months old
 Child 18 months old
 Child 3 years old
 Child 5 years old

Cc.
 1
 From 2 to 3
 4
 From 4 to 8

The adult dose of the plain fluidextract is 15 to 60 minims (1-4 cc), but this preparation is so bitter that it seems needlessly cruel to prescribe it for adults and children can hardly be made to take it at all.

Senna—This drug is more powerful than cascara sagrada and also much more prone to cause griping and general abdominal soreness. It is definitely contraindicated if there is intestinal inflammation of any sort. The dose of the fluidextract is $\frac{1}{2}$ to 1 drachm (2-4 cc), if taken at one time or 8 to 16 minims (0.5-1 cc), several times daily. Four to 8 minims (0.25-0.5 cc) of the tincture of belladonna added to each dose will antagonize griping. The U.S.P. syrup has a full dose of 2 drachms (8 cc). Such nostrums as "castoria" and "syrup of figs" which owe their chief value to senna should not be used. Senna may also be pleasantly taken as the U.S.P. compound glycyrrhiza ("licorice") powder, adult dose, 1 drachm (4 cc) or more, stirred up in water.

Dosage of compound powder of glycyrrhiza for children (Fantus)

Age of child	Gm
6 months	0.60
1 year	0.90
2 years	1.20
3 years	2.00
5 years	3.00

Aloe—The griping tendency of aloe is notorious. The U.S.P. pill contains 2 grains (0.13 Gm) and the official dose is 2 pills, which is likely to be too large. Fantus offered the following prescription:

R) Powdered aloe	gr xxij	15
Powdered soap	gr xxij	15
Mix. Make a mass and divide into 30 capsules.		
Label: 1 three times a day after meals.		

The active principle, aloin, should be reserved for use only when excessive action is needed, it may be given in a capsule containing $\frac{1}{2}$ grain (0.015 Gm).

Phenolphthalein—This is a yellowish white, odorless and practically tasteless powder, which has one great fault, namely, that a small dose sometimes acts excessively while a large dose many times fail to act altogether. Upon the whole, however, the drug is very reliable. It is usually given at bedtime and in the morning produces a stool very much like the normal. The adult dose is from 1 to 3 grains (0.06-0.2 Gm), infants of eighteen months may be given as much as $\frac{1}{2}$ grain (0.03 Gm). The National Formulary contains a cocoa and sugar flavored tablet containing 1 grain (tablets of phenolphthalein N.F.). A great many nostrums rely upon phenolphthalein for their principal or sole active cathartic ingredient, they are for the most part pleasing preparations but there is no good reason why the physician should not prescribe the drug in its Formulary preparation. A

sufficient number of skin eruptions have been shown to be due to the use of phenolphthalein to warrant one in taking this possibility into account in urticarias and erythemas, general constitutional effects, in which circulatory, renal, or nervous disturbances predominate, are much less often reported. Abramowitz thoroughly reviewed the work of himself and others on the subject, in 1935, and his paper, as well as the discussion which followed its reading leaves little doubt that the reactions are allergic in nature. Fantus and Dyniewicz, and Steigmann *et al.* of the same group, in studies between 1936 and 1938, showed that phenolphthalein is not excreted in the milk of nursing women, apparently does not disturb liver function, and would seem to require bile for its activity since it does not induce catharsis in individuals with obstructive jaundice and completely acholic stools. The prolonged use of large doses of phenolphthalein will many times aggravate a preexisting colitis and according to some authorities will even give rise to the condition in a previously normal bowel.

Salines—*Magnesium sulfate* (Epsom salt) very effective but objectionable in taste, Bethea (1936) says this may be largely overcome by dissolving the salt in one of the palatable fruit juices. A dose of $\frac{1}{2}$ to 1 ounce (15–36 Gm) is quite large enough. *Magnesium citrate* principally used as the solution of magnesium citrate which is available as an effervescent preparation in 12 ounce (366 cc) bottles, dose, 1 bottle or less, nauseating to many people and often quite violent in action. *Milk of magnesia* palatable and easy to give to children, also an antacid, laxative dose 2 to 4 drachms (8–16 cc) taken from the spoon or stirred in cold water, addition of fruit juice converts it in part into magnesium citrate which is more active (see above). *Sodium sulfate* (Glauber's salt) dose $\frac{1}{2}$ ounce (15 Gm), extremely nasty. *Effervescent sodium phosphate* mild but fairly pleasant, dose, 2 to 3 drachms (8–12 Gm) in water. *Compound effervescent powder* (Seidlitz powder) dose, the contents of one blue paper (sodium bicarbonate and Rochelle [potassium and sodium tartrate] salt) and of one white paper (tartaric acid), dissolved separately in water and then mixed, fairly pleasant in taste. *Sodium chloride* many individuals take about $\frac{1}{2}$ teaspoonful of common salt in a glassful of hot water on arising and repeat the dose once or twice while making the toilet, getting a good cathartic effect. This is supposed to be very clever and to teach us doctors something. I have been informed.

Liquid Petrolatum—Liquid petrolatum is bland, odorless, tasteless, and colorless, and can be taken from the spoon by most patients without any difficulty. It can be easily flavored however. Hinton has found that in 500 cc of the oil any one of the following flavoring oils is satisfactory: anethol, 10 drops, oil of almond 15 drops, oil of cloves 10 drops, oil of cinnamon 5 drops, oil of peppermint, 15 drops, oil of spearmint, 15 drops, and methyl salicylate, 25 drops. Fantus suggested that the oil combination used in the flavoring of aromatic elixir might be used to make liquid petrolatum aromatic, a combination of this sort would be oil of orange, 2 cc, oil of lemon 0.5 cc, oil of coriander, 0.2 cc, oil of anise, 0.05 cc, and liquid petrolatum, 1000 cc.

Emulsification lessens the oiliness of the substance and is said to combat the tendency to leakage. A number of proprietary brands of emulsified liquid petrolatum are now on the market and are well known to all. Of this class of preparations, Fantus wrote 'The worst that can be said about them is that

they are more expensive than the same quantity of liquid petrolatum, containing as they do from 25 to 60 per cent of the active agent. The dose of 1 tablespoonful is recommended for them with the suggestion that the activity of the emulsified oil is greater than that of the plain oil, a statement that remains to be proved."

Morgan (1941), in a paper read in the Section on Gastro-Enterology and Proctology at a recent meeting of the American Medical Association, severely castigated liquid petrolatum as a cathartic. His charges were that (a) it keeps the rectum partially full most of the time, causing its conversion into an abnormal receptacle for fecal material, (b) complete evacuation of the rectum is impossible for there always remains a tenacious layer of a dirty mixture of oil and feces covering the rectal mucosa, (c) absorption of carotene, and to a lesser extent of vitamins A and D, is seriously interfered with (parenthetically one might remark that Curtis and Kline, 1939, found carotene absorption interfered with only when the drug was taken several times daily before meals rather than in a single dose of 30 cc at bedtime), (d) digestion is incomplete because the passage of the contents through the bowel is hastened, (e) the healing of postoperative wounds in the anorectal region is delayed, (f) leakage from the anus may give rise to pruritus ani, (g) liquid petrolatum may be absorbed and cause pathologic changes in the abdominal viscera. It will be very interesting to see how well this thoroughgoing indictment will be upheld with the passage of time.

Yeast—Let us leave yeast to the quacks, certainly it is much less harmful than many another substance with which they dabble to the detriment of mankind.

Bacillus Acidophilus—Since the pioneer writings of Metchnikoff on the diettherapeutic role of lactic acid producing microorganisms, so many hastily set up claims have had to be abandoned, that I think the present attitude of skepticism which most scientists maintain toward the whole subject is not at all to be wondered at. However, we know now beyond doubt that *B. bulgaricus* cannot be implanted in the human intestinal tract and that it is even doubtful whether permanent implantation of *B. acidophilus* ever takes place. A number of very sincere workers have claimed that intractable cases of constipation, or diarrhea, or intestinal fermentation can be controlled or cured by the transformation of the intestinal flora from one that is predominantly gram negative to one that is predominantly gram positive—a number of other workers deny this, or at least have failed to succeed with the method. Kopeloff, who has been an indefatigable student of the subject, has found no correlation to exist between constipation and the absence of *B. acidophilus* in fecal specimens, about 50 per cent of individuals seem to harbor the organism. The aim of this type of therapy is, therefore, to implant the organism by feeding living cultures and at the same time to give large quantities of lactose to provide the preferred source of energy for the bacterium in the intestinal tract. The amount of the lactose necessary seems to be at least 1 to 3 ounces (30-90 Gm.), though much larger quantities are sometimes employed, the required amount of the culture is extremely variable. Weinstein *et al.* (1933) found that when successfully implanted the organism often persists for several weeks after the use of milk has been discontinued, they therefore favor long-continued treatment with periodic interruptions. The monograph of Rettger (1935) and his associates presenting

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the results of their many years of study, does not seem to me destined to win many advocates to this type of therapy. Most students feel that implantation can be brought about, if at all, only by the use of the milk preparations and not with such preparations as broth cultures, concentrated cultures, blocks, candies, tablets, or oil suspensions. The milk preparations are marketed in bottles; and should be kept on ice and consumed within the period of time stated on the label, the daily dose being the amount required to accomplish the desired purpose. 500 to 1000 cc is probably the average daily adult dosage. New and Nonofficial Remedies (1941) includes Cheplin's, Sheffield's and Supplee's *B. acidophilus* milks.

Treatment of Colic—Morphine or diluclid is of course contraindicated here because of the frequent recurrence of the attacks. Bastedo finds that castor oil by mouth and a hypodermic of codeine phosphate, $\frac{1}{2}$ grain (0.03 Gm.), and atropine sulfate, $\frac{1}{4}$ grain (0.001 Gm.), plus hot applications to the abdomen in the form of a hot water bag, electric pad, poultice or stupe (for method see Pneumonia), or a hot bath, will be followed by relief and sleep in most instances. If this fails, however, he irrigates, and if relief is still not obtained, puts the patient in the knee-chest position and slowly injects into the colon $\frac{1}{2}$ to 1 pint (250–500 cc.) of warm olive or cotton seed oil, the injection often being followed after a few hours by the passage of an abundance of mucus and the disappearance of the colic.

In some cases of colon consciousness there may be more or less constant pain though true attacks of colic do not appear, atropine sulfate, or the extract or tincture of belladonna in comparable dosage, is used by many men in such instances giving the drug three or four times daily for five or six days and then allowing the same number of days to elapse without it.

ULCERATIVE COLITIS

Ulcerative colitis is characterized by inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulceration predominates. This ulceration usually begins in the rectum and spreads upward eventually to involve the entire colon. It may, however, affect any one part, or several separated parts, of the tube. The course is in most cases a chronic one, extending over months and years, but the symptoms are not usually continuous during this time for there are often long periods of remission between severe attacks of the malady. The symptoms are fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus, and the passage of blood, mucus and pus. Distress from gas, and griping and other sensations along the course of the colon, are often experienced. Much weight is lost, a peculiar gray pallor is common, and varying degrees of anemia exist. In the very severe cases, the body has a peculiar odor and the face a hopeless expression. Barger has described a diplostreptococcus as the causative agent in the disease, but there are few who agree with him. Dack considers *B. necrophorum* the probable offender. Buttiaux and Sévin thought that certain organisms ordinarily regarded as saprophytic, such as *Escherichia*

coli, might under some circumstances have their virulence enhanced, but Nicholl's later study indicated that the assumption is probably gratuitous with regard to *E. coli* at least. *Endamoeba histolytica* and *Balantidium coli* have not been overlooked, but most observers feel it entirely unlikely that these parasites can be convicted. Many men in this field hold with Hurst, in England, and Crohn and Pelsen, in this country, who believe that ulcerative colitis is a form of chronic bacillary dysentery, the fact that *Shigella dysenteriae* cannot be uniformly cultured from the stools offering no embarrassment to this theory, since it is well known in the tropics that even in individuals with undoubted bacillary dysentery such culture is difficult after the acute stage is passed. Mackie's observations a few years ago led him to believe that complex deficiencies, not only in vitamins but in biologically complete proteins and in electrolytes as well may constitute an essential part of the underlying mechanism of the disease. The possibility that allergic factors are important in the etiology is presented by Hare. Mackie and Andresen, each upon the basis of independent observations. There is also considerable evidence of a psychogenic background in some of the cases.

THERAPY

Rest—It would seem that all authorities, whatever their disagreement on other points, are unanimously of the opinion that the patient should be maintained at complete rest in bed so long as there is fever and more than two or three stools daily.

Diet and Vitamins—Donald and Brown (1940), of the Mayo Clinic, say with regard to victims of this disease that one fundamental fact is certain, their chances for recovery depend greatly on the availability of the best possible quality of food. Protein is the most important article, chiefly in the form of red meats, liver, kidneys, sweetbreads and lean pork. They say that since fruits and vegetables may add too much residue to the diet and increase the number of bowel movements, restriction of these articles requires supplementary use of ascorbic acid and all the fractions of the B complex (see the Deficiency Diseases). Cheney (1939) has been reporting the satisfactory initiation of remissions by the injection of liver extract as in pernicious anemia, believing that the effective factor is probably some as yet unidentified substance in liver. Very recent observations indicate that vitamin K may be deficient in some cases (see Vitamin K Deficiency).

Sulfonamides—It does not seem to me that the record of these agents in colitis is very distinguished, for example, Collins (1940) obtained what he considered a favorable response in only about half his 26 cases. In view of the good results reported with sulfanilylguanidine in some of the frankly infectious diseases of the intestinal tract, one might be hopeful that this agent especially would prove spectacularly helpful in ulcerative colitis, but in the recent thorough study of the matter by Stickney *et al.* (1942) at the Mayo Clinic, this hope was not entirely fulfilled, some of their 46 patients did experience improvement or arrest of the disease, but they felt that in view of the great variability in the course of this malady it was not possible to state with certainty that the drug had been responsible for the improvement in these instances.

Vaccines and Serum—Believing that the majority of cases are the result of infection with dysentery bacilli, Hurst (1935-1936) uses polyvalent anti-

dysentery serum After preliminary desensitization, 20, 40, 60, 80, and 100 cc. are injected intravenously on consecutive days, sometimes a few additional doses of 100 cc are given The experience of Crohn and Rosenak (1935) convinced them also of the superiority of this type of treatment Bagen has prepared a vaccine with the organism that he considers causative and has also used a serum prepared by immunization of the horse

Diarrhea.—Early in all cases some attempt is usually made to control the diarrhea, though it is a fact that such success as rewards these efforts is nearly always only temporary The following drugs are usually tried out in succession

Bismuth subcarbonate, 20 to 30 grains (1.5–2 Gm) every three hours

Bismuth betanaphthol, 10 grains (0.6 Gm) every four hours

Calcium carbonate, 15 to 30 grains (1–2 Gm) every four hours

Calcium glycerophosphate, 10 to 15 grains (0.6–1 Gm) every four hours

Acetyltannic acid (tannigen), 3 to 10 grains (0.2–0.6 Gm) every four hours

Protan, 20 to 30 grains (1.3–2 Gm) every two hours

Colic—During the course of a severe attack, hot stupes applied to the abdomen, according to the method described under Pneumonia, often bring relief, morphine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.008–0.015 Gm), or dilaudid, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.0013–0.002 Gm), or preferably codeine, 1 grain (0.065 Gm) may be needed, of course paregoric in usual doses could also be used Hurst gives tincture of belladonna every six to four hours, increasing from 5 minims (0.3 cc) to the maximum amount that can be taken without uncomfortable dryness of the mouth resulting He finds a tablespoonful of charcoal several times daily also helpful Bagen and Jackman (1939) find that the addition of $\frac{1}{4}$ grain (0.02 Gm) of papaverine hydrochloride to an opiate atropine mixture is helpful

Local Applications—Attempt is often made, by means of antiseptic enemas or topical applications, to bring about healing of the ulcers the details of such locally applied therapy are discussed in the article on bacillary dysentery It should be remembered that the tissues are highly sensitive to trauma in colitis and overloading with excessively large retention enemas should therefore be avoided, and the soft catheter should be introduced only just beyond the anal sphincter Eyerly and Breuhaas (1938) follow a cleansing enema in one hour with a retention enema consisting of 3 to 5 ounces (90–150 cc) of 3 per cent aluminum hydroxide and 15 per cent kaolin in colloidal suspension mixed with an equal amount of sterile distilled water the patient retaining this as long as there is no discomfort Best (1937) used daily rectal injections of 2 to 4 ounces (60 to 120 cc) of cod liver oil

Intestinal Oxygenation—Felsen (1931–1936) studied the effects of altering the gaseous tension in the intestines by the rectal introduction of oxygen Experience showed that the average acutely ill adult will tolerate 250 cc (measured by water displacement as it comes from the tank) given alternate hours between 8 A.M. and 8 P.M. Passage through warm water heats the gas which is then allowed to enter through an ordinary soft rubber catheter introduced only a few inches There is moderate distention of the bowel as far as the pylorus but much of the gas is apparently rapidly absorbed since very little is ejected from the rectum Felsen believes that this treatment leads to the diminution of spore-bearing anaerobes, encourages the superficial

growth of obligatory or facultative aerobes, and favors a homogeneity of intestinal flora, the effect of oxygen on the intestinal tissue proper is even more speculative. Forty cases thus treated, with adequate controls, were apparently much benefited.

Calcium and Parathyroid.—Haskell and Cantarow (1931) used these drugs with satisfaction in 9 of 10 patients. Calcium lactate, 30 grains (2 Gm) or calcium gluconate, 60 grains (4 Gm), orally three or four times daily, three and a half to four hours after meals, the patient being cautioned not to eat between meals, 20 to 30 grains (1.2–2 Gm) of ammonium chloride was given with the calcium salt to increase its utilization by raising the hydrogen ion concentration of the tissues. Parathyroid extract was injected intramuscularly, 20 to 30 units, at intervals of forty-eight to seventy-two hours. Reporting again, in 1935, they said that 5 of the patients had remained essentially symptom free for periods of two to six years, relapses occurred in 2 instances, but the patients again responded to the treatment, 1 patient died of pneumonia after remaining well for three years. In an additional 16 cases treated for six months to four years, 8 became clinically well, 7 were much relieved, and 1 was not benefited.

Transfusion and Iron.—Several observers feel that blood transfusions have been of great value in many of their severely ill patients. Benson *et al* (1942) say that at the Mayo Clinic they feel that these chronic ulcerative colitis patients are more liable to transfusion reactions than ordinary post-operative or anemic patients. If he can get it, Telsen (1936) prefers to use the blood of a donor who is known to have recovered from bacillary dysentery. Garvin and Barger (1937) find it of value to administer iron also.

Allergic Factors.—Investigation from this standpoint should be worth while in all cases. Andresen (1942) found food allergy to be the principal cause of the ulcerative colitis in 33 of this series of 50 patients. However, Mackie (1942), while believing allergy to be very important, thinks it is often only a secondary factor, i.e., a local sensitization developing upon a tissue previously inflamed through the operation of some other factor.

Bacteriophage and Antivirus (Besredka).—These are among the things that are used. I have placed the following papers in the Bibliography: MacNeal *et al* (1934), Oesterlin *et al* (1935), Winkelstein and Herschberger (1935).

Surgery.—Ileostomy is sometimes a life saving measure in severe cases but the results are often poor and resort to the operation is furthermore surely a confession of defeat. Streicher (1942), summarizing his own experience and that of one hundred specialists whom he consulted by questionnaire, says that the operation should be performed only upon those patients in whom the colon has undergone irreparable damage. Partial or complete colectomy is sometimes performed. Appendicostomy, or cecostomy, with subsequent daily washings for an hour (normal saline, twenty minutes 1–2 per cent tannic acid solution, twenty minutes, normal saline, twenty minutes), is sometimes preferred. According to Hurst, some English surgeons recommend appendicostomy in almost every case, but he deplors such routine surgery. Mackie (1938) is of opinion that neither appendicostomy, cecostomy nor double-barreled colostomy have a place in the surgery of this condition.

HEMORRHOIDS

Internal hemorrhoids are masses of redundant tissue caused by the dilation of capillaries, arteries or venules just inside the anal sphincter. They cause trouble either by reason of the fact that they are ulcerated and thus give rise to considerable pain when scraped by the feces, or by their bleeding, or by their prolapsing which necessitates frequent manual replacement up behind the sphincter, or by the fact that they become strangulated after having passed out through the sphincter. The so-called "external" hemorrhoids are really only tags of skin that are vascular and that become troublesome when inflamed. A great deal of anal itching is usually associated with hemorrhoids.

THERAPY

Palliative Measures—Prolapsed hemorrhoids are best sprayed with cold water, or a cold compress may be applied, in order to reduce the congestion. They may then be gently returned through the sphincteric canal by manipulation with the oiled fingers. Other palliative measures than this I think are no longer justified in view of the excellent results now to be attained by employment of either of the two curative measures, however, of the following prescriptions, the first is for an astringent rectal suppository, the effect of which can be modified by changing the proportion of tannic acid.

R ^j Tannic acid	gr xv	1 0
Balsam of Peru	℥xxij	1 5
Bismuth subcarbonate	℥iiss	10 0
Oil of theobroma (cacao butter)	℥iv	16 0
Cerate	℥ss	2 0
Make 10 suppositories		
Label 1 three times daily		

And the second is for an analgesic suppository

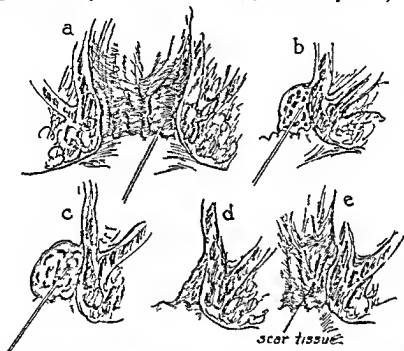
R ^j Powdered opium	gr vij	0 4
Extract of belladonna	gr ij	0 12
Ethyl aminobenzoate	gr xviii	1 2
Oil of theobroma (cacao butter)	℥iij	12 0
Make 6 suppositories		
Label 1 before bowel movement		

For treatment of the itching see Pruritus Ani

Surgery.—It is now urged by surgeons that internal hemorrhoids which are causing discomfort be removed by operation, a plea that is heartily endorsed by most nonsurgical practitioners since the operation is practically always successful, is not dangerous, does not incapacitate for a long period though the patient suffers much immediate postoperative pain, and often cures a stubborn constipation as well as the case of piles.

Injection.—External hemorrhoids must never be injected. It is now the consensus that the injection treatment may be employed with fair hope of affording relief to patients whose internal hemorrhoids are small or medium sized and not accompanied by infection, thrombi, pain, muscle spasm, or marked prolapse. Bleeding is nearly always stopped, but in many instances the relief obtained through injection is not permanent. The patient presents for treatment with the rectum empty, and during the period of the treat-

meats should avoid the use of strong purgatives, obtaining a daily bowel movement by the use of mineral oil or a mild drug such as phenolphthalein if necessary. Enemas are not considered advisable while the treatments are being given. Haskell (1939) finds that placing the patient on the side in the Sims or a similar position and the preliminary partial dilatation of the sphincter by inserting the finger before introducing a tubular anoscope of the Martin type, is the best procedure. Usually 1 to 2 cc of the sclerosing solution is injected through a long needle of small caliber, injecting one or two areas at a time and spacing injections about a week apart. The technic of employment of the solution is shown in the illustration below (reproduced through the courtesy of Dr. Neil W. Swinton, of the Lahey Clinic)



Technic of injecting hemorrhoids (Swinton, N. W., Surg. Clin. N. A., 19 669 1939) a, the needle inserted into the internal hemorrhoid well above the anocutaneous line and deeply into the hemorrhoid b, a cross section showing the tip of the needle in a perivascular position c, the distention of the internal hemorrhoid d and e, the resultant scarification.

Quinine and Urea Hydrochloride—Perhaps this solution, popularized by Terrell is still the one most often employed. For the average case 5 per cent strength is used but 10 per cent is occasionally used in recalcitrant cases.

Phenol—This agent seems to be greatly preferred in England and is also gaining favor in the United States. Swinton (1939) wrote that after a comparative study he favored it. The usually employed preparation is 5 per cent phenol in almond, olive or cotton seed oil.

Alcohol—Alcohol seems to be preferred to anything else on the Continent, but it had very little vogue in our country because of the transient fever subsequent hemorrhages and occasional necroses which follow its use, some years ago Boas reported the practical elimination of these reactions through reduction in the concentration of the alcohol from absolute or 95 per cent, to 70 per cent.

PROCTALGIA FUGAX

(Spasmodic High Rectal Pain)

Shortly before his untimely death, in 1936, Dr Th E Hess Thaysen of Copenhagen, recorded a series of cases of fleeting but severe rectal pain unassociated with other signs or symptoms, to which, with due apology for the philologic heresy of coupling a Latin adjective with a Greek substantive, he gave the name "proctalgia fugax." The flood of communications "to the editor" which followed the appearance of his paper, together with many conversations among physicians, have amply confirmed not only the existence but the frequent occurrence of this entity. The sufferers are usually adults and apparently more often males than females, there is no associated rectal or anal pathology, nor is there any evidence that the malady affects or is affected by intercurrent diseases, or that it shortens the duration of life. The victims merely suffer at varying intervals, oftentimes through a long series of years, fleeting attacks of excruciatingly severe pain, whose site is practically always indicated to be within the rectum just above the anal sphincter. In his Croonian lectures on the visceral neuroses, in 1930, Ryle included mention of 15 cases of proctalgia fugax, and Lauda, in Vienna, reported a group of cases in the same year (not knowing in fact, that the entity had been previously described). Apparently a large proportion of the 100 cases of high rectal pain which Buie and Brust analyzed, in 1934, were of this sort, it seems that MacLennan also described the condition as long ago as 1917. Characteristic features of an attack are the following: (a) Beginning often with a sensation of pressure high up in the rectum lasting a few moments the pain develops rapidly to quite agonizing proportions, and then recedes slowly during several minutes, the average total duration is ten to fifteen minutes although attacks not infrequently last longer and now and then seem to be aborted before reaching full force. (b) The patient may gasp for breath and experience some degree of substernal tightness but these manifestations seem to be not the rule, occasionally also there is sweating, pallor, and momentary loss of consciousness. (c) The pain seldom radiates and the attack is neither preceded, accompanied nor followed by any disturbances of intestinal function (distention, tenesmus, constipation, or diarrhea). (d) An attack begins unaccountably at any time of day or night and seems to be unrelated to the state of rest or activity in which the patient finds himself at the moment. (e) Association with coitus, masturbation, migraine and epilepsy has been reported, but certainly in the majority of cases no such relationship has been established. (f) In the few recorded instances in which physicians have made digital examination of themselves during attacks anal spasm has not been observed, and it has been noted by numerous patients that the stool may be passed with accustomed ease during an attack, though it is said that after defecation the pain sometimes seems to be accentuated in degree and extended in duration.

THERAPY

There is really very little to describe for it is apparent that physicians, though well aware of the existence of this peculiar malady, have been treating it in the traditional fashion of the ostrich, both in themselves and in their

patients Perhaps now that it is brought out into the light and fully faced someone will give it the serious study it appears to deserve

Local Treatment—Of course the whole gamut of local measures—belladonna suppositories, hot applications, and so on—has been run, but with poor results Both Marshall (1935) and Ryle (1939) have cited single instances of a patient who obtained quick relief through inflation of the rectum with air, I should think that this could be easily accomplished with the ordinary rubber bulb ear syringe, usually at hand as a denizen of a dark corner in the bathroom medicine cabinet

Postural Change—Thaysen recorded a patient who found it helpful to lie flat on the belly, another on the back, a third on the side, a fourth sat on the edge of a hard chair Smith's (1935) patient was relieved by the adoption of a completely doubled up squatting position with finger tips touching the floor, apparently the ordinary position of defecation does not provide sufficient flexion

Allergic Factors—It seems to me that it has taken the allergists a long time to learn that Thaysen has raised this condition to a position of respectability since there would seem a fair chance that they might reasonably claim it for their own Several years ago Bramigh (1935) obtained relief in 2 cases by use of Rowe's elimination diets

Tobacco—Several years ago a case was recorded in which the physician, arguing the analogy between these attacks and those in "pseudo" angina pectoris, had the patient stop smoking with resultant complete relief Ryle (1939) seems to investigate the smoking habits of his patients, but records only one instance in which the patient stopped smoking, other adjustments were made in this patient's life at the time, but it is noteworthy that the attacks ceased to occur However, proctalgia fugax also occurs in nonsmokers

Amyl Nitrite—Marshall's (1935) patient obtained as certain, quick, and complete relief from amyl nitrite as does the angina sufferer "A few seconds with a capsule and a handkerchief at the side of the tennis court, or in the cloak room at a dance, and all is well and he can rejoin his party"

EPIDEMIC VOMITING AND DIARRHEA

(Acute Infectious Gastro-enteritis, "Intestinal Influenza")

Increasingly in recent years there have been reported outbreaks of an apparently infectious and contagious acute gastro-intestinal malady usually referred to colloquially as "intestinal flu" I have seen reports of these epidemics in England and on the Continent as well as in the United States, most probably they occur elsewhere also Usually the epidemic appears and disappears rather suddenly but may persist at its peak in a given locality for several weeks The number of cases is often very high, as for example here in Milwaukee in the spring of 1936, when it was thought we had more than 100,000 cases—I doubt the figure, but at any rate a good many people were sick with this malady at about the same time Fortunately, the mortality is very low, indeed the primary mortality seems to be practically nil

The characteristic symptoms are sudden onset of nausea, vomiting, abdominal cramps, watery diarrhea, slight headache and general aching, weakness, some fever, and a general feeling and often appearance of a considerable degree of prostration. In various outbreaks one or other of the symptoms seems to predominate, for example, there is sometimes considerable vomiting without diarrhea, while at other times abdominal cramps and profuse and debilitating diarrhea are seen to the exclusion of most of the other symptoms. Some patients are afebrile, others have grippal symptoms. In most instances the duration seems to be between two and five days, recovery occurring quickly and without sequelae, relapses and second attacks, however, are of frequent occurrence.

No organism has been consistently recovered from any of the excreta and identified in a probable causative role in this disease. Here in Milwaukee, as elsewhere, we have indulged in a certain amount of discussion of a possibly contaminated water supply, but nothing definite has come of this. There are of course those who hold that the disease is of virus origin and that infection occurs by the droplet route, but their case is by no means established either.

THERAPY

No specific therapy is at hand of course. In fact, since the condition is self-limited it does not seem to me sensible to attempt to do a great deal more than merely wait. Several years ago, Wildman (1933) said that milder cathartics are not effective, that magnesium sulfate and mineral oil both aggravate the condition, but that castor oil in full dose in the beginning might be helpful—he said actually that he found ‘no drug to compare with castor oil’ but he did not specifically say to compare with it for what, presumably general relief of the whole distressed state was meant. He also liked to give a cleansing saline enema and, if there is much nausea or vomiting, to precede the castor oil and enema about fifteen to thirty minutes by 1/100 to 1/50 grain (0.0000 to 0.0012 Gm) of atropine sulfate hypodermically.

Greenthal (1936), discussing his experience of cases among children here in Milwaukee, says he knows of no measure which will relieve the severe vomiting in the beginning, but total abstinence from food and water for a few hours is probably advisable, however, if fluid is desired he allows a few sips at a time of water, weak tea, carbonated beverages, cereal gruels, and fruit juices, but not milk or broth. Heat to the abdomen is often very soothing, and of course after sufficient time has elapsed so that one is certain he may not mask a more serious abdominal disorder, paregoric or even the stronger opiates may be used if still needed. After subsidence of the more acute symptoms, Greenthal places his children on a high carbohydrate diet—omitting milk, eggs, meats and soups and giving sugars and starches freely—and finds that the diarrhea usually responds promptly to this regimen. In some cases he has used the apple diet (see Index) with good results. Return to milk must be postponed for some time as it seems often to cause a relapse.

DISEASES OF THE LIVER AND BILE PASSAGES

DISEASES OF THE LIVER AND BILE PASSAGES

JAUNDICE

In approaching jaundice differentially it should be remembered that almost all the types of liver and bile duct disease may produce jaundice with little or no pain. Chronic pancreatitis, carcinoma, hemolytic jaundice and several of the other anemias, familial nonhemolytic jaundice, and Weil's infectious jaundice are to be ruled out. Eppinger (1937), and more recently Kirschbaum and Popper (1940), have described a few cases of a fulminating fatal form of toxic hepatitis which appears to be an intermediate stage between acute infectious hepatitis (catarrhal jaundice) and acute yellow atrophy. In lobar pneumonia, jaundice is probably always latent but may appear clinically, it may sometimes be seen in relapsing fever, in congenital or acquired syphilis in sepsis and tuberculosis, and it is often present in malaria and always present in yellow fever. Many chemical poisons may cause toxic hepatitis and jaundice: arsenic, antimony, acetic acid, carbon tetrachloride, cinchophen, chloroform, dinitrophenol, phenylhydrazine, potassium chlorate, phosphorus, picric acid, snake venom, mushroom poison, trinitrobenzene, tetrachlorethane, trinitrotoluol. It may appear in eclampsia and following accidental or operative trauma, it may arise from any one of a number of mechanisms in chronic heart disease (its sudden appearance in myocardial insufficiency points toward pulmonary infarction), and it is one of the symptoms following the transfusion of incompatible blood. The ordinary icterus neonatorum is physiologic, being a reflection of the presence in the blood of an increased amount of bilirubin resulting from hemolytic destruction of surplus erythrocytes, the etiology of the rare but usually fatal icterus gravis neonatorum, and the even more rare and fatal Winkel's disease, is still unknown.

Such of the above entities as come within the province of this book are taken up at sites too numerous to list here, the reader is referred to the table of contents and the index. But when all of these have been differentially ruled out there remains a type of case usually designated "catarrhal jaundice" but perhaps more accurately described as "acute infectious hepatitis", under the latter designation this entity will be described below.

ACUTE INFECTIOUS HEPATITIS

(Catarrhal Jaundice)

This malady is principally encountered in children and young adults and more often in males than in females, though middle aged and even elderly patients are not rare. There is little accurate information regarding the pathology of the affection for it is rarely fatal and the autopsy material upon cases suffering an accidental death is too small and contradictory to be of much

value. However, in recent years Hurst and Simpson (1934) have divided cases into two groups: one, those due to a mild primary hepatic necrosis, and the other, those due to temporary obstruction of the bile passages. The latter group would comprise those cases in which it is assumed that there is a gastroenteritis with a "catarrhal" condition of the mucosa of the upper gastrointestinal tract and the bile ducts and with the ampulla of Vater plugged with mucus. It is the opinion of Cullinan (1939) that both types of pathology probably characterize cases in a given epidemic.

The symptoms of acute infectious hepatitis (catarrhal jaundice) are malaise, sometimes mild headache and dizziness, enlargement of the liver and sometimes of the spleen, occasionally pain in the liver region, nausea and perhaps vomiting—both these latter symptoms being especially marked if the patient refuses to go to bed—slight fever, or normal or subnormal temperature, slow pulse, jaundice, bile-stained urine and clay-colored stools, more or less general pruritus, and mental depression which is sometimes quite profound and is not infrequently associated with an unwonted irritability. The gastric symptoms usually persist for only a few days, but many patients suffer on return of nausea and dizziness if they attempt to assume the upright position at any time throughout the course of the malady. The duration of an attack is from ten days to three or even six weeks, and some degree of jaundice often persists for a long time in a patient otherwise apparently quite recovered. Occasionally the attack recurs. Several observers are now in agreement with Soffer and Paulson (1934), whose studies indicated that possibly permanent impairment of hepatic function occurs more often than has heretofore been suspected. In epidemics observed in the United States and in England, Norton (1939), Pickles (1939), and Cullinan (1939) find the incubation period to be between twenty-one and forty-five days. Cullinan, however, says that Glover, who has made a considerable study of this disease, feels that the incubation period may be in some instances no longer than four days. Pickles has proved contagion on the fifth and seventh days and thinks there is some evidence of contagiousness before the onset of symptoms. Both he and Cullinan have acted successfully on the assumption that two weeks' isolation is sufficient in children; the latter does not hesitate to admit adult patients to general wards when jaundice is once established. Dietary indiscretions, the abuse of alcohol, and exposure to cold were often formerly mentioned in the etiology of this type of hepatitis, but the causative role of none of these factors was ever convincingly shown. Now that the epidemic nature of the disease and therefore its almost certainly infectious nature, is generally acknowledged there is much talk of a virus and droplet respiratory infection, but the evidence is still presumptive.

THERAPY

That portion of the therapy which is based upon the assumption that there is in most cases a subacute inflammation of the stomach and upper small intestine is usually directed toward the diet, local analgesic action over the liver, and drainage of the gallbladder. In some cases in addition it is certainly wise to proceed upon the assumption of the occurrence of considerable hepatic insufficiency and proceed accordingly (see Portal Cirrhosis below). Bile salts and vitamins are also rationally employed.

Diet.—A light soft diet, high in carbohydrates, low in proteinas, and practically devoid of fats, is usually prescribed. Toast, gruels, junket, custards, rice pudding, cereals, fruits, and vegetables are all permitted in small quantities. Most clinicians feel that milk should be withheld or that only skimmed milk should be given.

Drainage of the Gallbladder.—It is the general practice to start off with a dose of calomel and then to keep the bowel open with a daily saline purge, the idea being of course that the cathartic salts tend to cause opening of the sphincter of Oddi and reflex contraction of the gallbladder. But for a bed-ridden patient, who is not obtaining great quantities of food, large doses of salts are necessary to induce defecation, and the evidence that much biliary drainage is accomplished in this way is not convincing.

Another attempt to improve biliary drainage through provoking an alteration in mucous membrane secretions consists in the use of ammonium chloride in about 7½-grain (0.5 Gm) doses, as in the following prescription, I doubt that this therapy is worth anything.

R	Ammonium chloride	℥iv	15 0
	Syrup of citric acid	℥j	30 0
	Water to make.	℥iv	120 0

Label. Teaspoonful in water three times daily after meals.

Nonsurgical drainage of the gallbladder (Lyon duodenal tube method) is said to be very often of great value.

Local Analgesia.—Hot applications over the liver region are felt to be of value in some cases; perhaps fomentations (stupes) are sometimes to be preferred to the hot water bag, but it seems needlessly hectic therapy to force this sort of thing upon the family attendant when the patient is no more dangerously ill than is usually the case in catarrhal jaundice.

Miscellany.—Some physicians still give calcium salts but probably without effect. Bile salts, since they are usually not present in very large quantities in most cases (witness the clay-colored stools) are rationally employed, more especially as recent work is showing that certain of the vitamins are poorly absorbed in the absence of bile. The vitamins themselves are also indicated. Breese and McCoord (1940) have shown that vitamin A is poorly absorbed in catarrhal jaundice and there is also evidence that vitamin B complex improves liver function. Of course if there is evidence of a bleeding tendency, or perhaps even if not, there is the indication for administration of vitamin K. The methods of employing all the vitamins are discussed elsewhere in the book (see Index). Relief of itching is discussed under Portal Cirrhosis.

BLEEDING IN OBSTRUCTIVE JAUNDICE

(See *Vitamin K Deficiency*)

THE CIRRHOSIS

The study of the cirrhoses of the liver has only recently been taken up again with vigor after having been neglected for a very long time. Anyone, therefore, who writes upon the subject today must do so with the knowledge that tomorrow, or perhaps the day after, all that he has to say may be shown to be quite wide of the truth, for much has been learned in recent years. "The subject is ripe for investigation," says Rowntree, "it awaits the touch of a Richard Bright." But, pending the arrival of the new Bright, I must content myself with a more or less conventional listing of the entities.

The cirrhoses, then, may be divided into (a) portal, (b) syphilitic, (c) Hanot's, and (d) obstructive biliary. Of these types, it may be said that Hanot's, if it really exists as a disease entity, is of so rare occurrence that it cannot be dealt with in this book (the same statement regarding rarity applies also to Banti's disease, Wilson's disease, and hemochromatosis, in all of which cirrhosis forms a part of the picture). The syphilitic affections of the liver were dealt with in the article on Syphilis; it should be noted, however, that portal cirrhosis may occur in an individual who also has syphilis, *i.e.*, every case of cirrhosis in a syphilitic is not necessarily a case of syphilitic cirrhosis. Obstructive biliary cirrhosis occurs as a complication of chronic gallbladder disease and is relieved or not accordingly as the measures directed toward the cure of the gallbladder condition succeed or fail, or it may result from congenital deformities in the biliary system, also there is an infantile form of biliary cirrhosis apparently peculiar to certain regions in India and thought likely to be a reflection of dietary deficiencies in the mother. Portal cirrhosis then, alone requires separate consideration, which it is given in the section below.

PORTAL CIRRHOSIS

The clinical entity which we recognize as portal cirrhosis results from prolonged inflammatory, degenerative or proliferative changes in the liver which are believed to occur in the following sequence: (a) degeneration of cells in the periphery of the lobules caused by poisons carried in the portal vessels, (b) proliferation and contraction of interstitial tissue about the remaining cells and the bile ducts which attempt repair by means of a resort to hyperplasia, and (c) portal obstruction and the more or less successful attempt to overcome it by the establishment of a collateral circulation. The surface of the liver is usually 'hob-nailed' and the organ diminished in size, but it may be enlarged and smooth due to the deposition of fat. The spleen is also frequently enlarged whether merely by reason of venous congestion or because the liver is not an isolated organ but exists as part of a 'spleno-hepatic' system is not known. Infections, toxins, overactivity of the liver, the excessive deposition of pigments—any one or all of these factors may be the causative agent in a given case. Bloomfield's (1938) opinion based upon considerable study of cases over a period of years is one in which most clinicians undoubtedly concur: to wit, cirrhosis is usually the terminal stage of a long disease which runs most of its early course without clinical symptoms. Excessive use of alcohol has long been blamed for the production of most of the cases, but Mallory (1933), who investigated the matter both clinically and experimentally for many years, was of opinion that it might be phosphorus as a contaminant, rather than alcohol itself which causes the

disease Von Gerlach (1935) found the copper content of cirrhotic livers relatively high and thought that this mineral in conjunction with alcohol might be of significance in the causative role Moon (1934), reviewing the literature, finds that a rather large number of substances may induce experimental cirrhosis, very interesting, from the clinical standpoint, is the fact that nicotine may be one of these Boles and Clark (1936), studying the records of 4000 autopsies at the Philadelphia General Hospital, concluded that alcohol is not a specific causative factor, but Evans and Gray (1938) deduce from the cirrhosis records among more than 17,000 autopsies at the Los Angeles County Hospital that 'the excessive consumption of alcoholic beverages seems to be a contributing factor' Connor (1939) feels there can be little doubt that alcohol and the habits induced by the consumption of large amounts of alcohol are the most important factors in the production of fatty liver which passes on in some cases into cirrhosis, his studies indicate that the factor next in importance to alcohol itself is the abnormal diet which invariably accompanies severe chronic alcoholism, and he thinks one may further reduce this to a specific lack of sufficient carbohydrate in the diet Hall and Morgan (1939) give their opinion as follows, as the result of careful study of a considerable series of cases in which alcoholism was the most common clinical factor The patient with chronic alcoholism suffers from low intake of carbohydrate, greatly diminished storage of glycogen, fatty replacement of the liver, and deficient intake of vitamins These conditions render the liver especially vulnerable, so that continued abuse of alcohol is followed by necrosis of liver cells and fibrosis, which in the susceptible patient after years results in cirrhosis We believe that in the majority of cases the enlargement and fatty infiltration of the liver constitute the first development, that this passes imperceptibly into the subacute phase of cirrhosis, to be followed later, if the patient survives long enough, by the appearance of the small hobnail liver A small percentage of the patients die during the subacute stage as a result of complicating infections, dietary deficiency diseases, hepatic insufficiency, portal hypertension, alcoholic psychoses, and other disorders We believe the term 'alcoholic cirrhosis' has a firm basis in etiology " Patel's studies in recent years are certainly pointing toward definite vitamin A and B-complex deficiencies in so-called alcoholic cases However, cirrhosis does also undoubtedly occur among nondrinkers, not only alleged nondrinkers in regions of high alcohol consumption, but likewise among peoples who do not drink at all, as was shown by Yenikomshian (1934) with regard to the nondrinking populace of Syria and the Lebanon, and by others for several of the Far Eastern peoples Attempts to correlate statistically a rise or fall in cirrhosis incidence with the alcohol prohibitive measures that have been tried out in various parts of the world are worthless, all countries having explicitly or tacitly admitted that such measures notoriously fail to control alcohol consumption It has been alleged that beer is less prone to cause cirrhosis than wines and 'hard' liquors There the matter stands—still controversial, but it seems to me that the supporters of the alcoholic side of the argument are beginning to win again

Portal cirrhosis occurs most frequently in the early forties and terminates fatally in the early fifties Men are more frequently affected than women in about the proportion of 2 to 1 The early symptoms are dyspeptic and are rarely recognized, though the new tests of hepatic function, of which the hippuric acid test of Quick seems to be the best, should make diagnosis easier

now than it was a few years ago. In a fully established case the patient has lost much weight and energy, has a muddy complexion, sunken eyes, and a sharp nose on which there are distended venules, he complains of dyspepsia and perhaps of hemorrhoids and of an intensely itching skin. Engorgement of the veins in the abdominal wall and elsewhere is a striking evidence of the attempt that is being made to establish a collateral circulation. Ascites occurs in more than 50 per cent of cases, the abdomen sometimes containing as much as 15 liters of fluid. Both the spleen and the liver may be found to be enlarged. Full jaundice is unusual, but the urine is usually scant and highly colored, in some cases there is a pernicious like anemia. Purpura and a tendency to easy bleeding are very common, and profuse hemorrhage from the stomach, due to the anastomoses formed about the lower end of the esophagus is a frequent and serious occurrence. In far advanced cases such symptoms of hepatic insufficiency as malaise, nausea and vomiting, headache, depression, loss of memory, and delirium or coma may be seen. The majority of patients do not die from hepatic insufficiency directly, however, but from complicating disorders, such as circulatory failure, hemorrhage, ascites, and intercurrent infectious disease, particularly pneumonia or a rapid tuberculosis.

John Brown described a case of cirrhosis in 1685, John André in 1788, and Matthew Baillie in 1818, both wrote on the subject, but the first adequate account was that of Laennec, who gave the disease its name in 1819.

THERAPY

Diet—It is of course imperative that alcohol be denied the patient, but in the case of habitual heavy drinkers it may sometimes be advisable to withdraw the drink by rapid diminution in the quantities allowed rather than by the more radical procedure of cutting off all the supply at once. Nowadays since full recognition has been had of the protective value of carbohydrate, it has become the usual practice to give a high carbohydrate low protein diet—350 Gm. or more of carbohydrate, 1 Gm. of protein per kilogram of body weight (food value tables in Diabetes) and just that amount of fat which the patient will require to make the diet palatable, i.e., usually small amounts of butter and cream. However, even though the patient takes large amounts of carbohydrates as jellies, jams, syrups, candy, and sweetened fruit juices, it is often impossible to get enough into him by mouth for full protective value, in which instances of course supplementary dextrose must be given intravenously (see Hepatic Insufficiency below). Eggs, spices, condiments, fried foods, fat meats, and vegetable oils are not permitted at all. The frequent drinking of small quantities of mild saline water has long been looked upon as of value in depleting the portal circulation, and many of the older generation of practitioners believed that it was the mineral waters that caused their patients to be temporarily improved while sojourning at a spa, but many of us now take the liberty of believing that the psychic effect of such a sojourn is its most valuable contribution to therapeutics—though who can be certain that we are not wrong?

Vitamins—As stated in the introduction, Patek and his associates have been showing that good results may often be expected to accrue from the use of large amounts of the vitamins, particularly vitamin A and the B complex. Vitamin A may be given as one of the fish liver oils, and the B complex in the form of the synthetic preparations (see Pellagra). Some

men prefer to give a good preparation of brewer's yeast which is alleged to contain, in addition to the vitamin B complex, a theoretical factor "X," the absence of which is considered to cause experimental cirrhosis. In addition to vitamin A and some source of B complex as above, some men also inject liver extract.

Iodides—Iodides are often employed, as in the treatment of syphilis, in the hope that the overgrowth of connective tissue might thus be corrected, but I do not know that the survival of this practice rests upon any more secure footing than the rather vague clinical impression that it is of some value. It is of course an extremely difficult matter to put to the test of controlled clinical experimentation.

Focal Infection—It is generally agreed that all demonstrable foci of infection should be eradicated if this can be accomplished consistently with the safety of the patient, that such treatment serves to arrest the progress of the disease can rarely, if ever, be shown, for whatever contribution the infectious process may have made toward the establishment of the disease has become accomplished long before the diagnosis of cirrhosis is made.

Dyspepsia—In the beginning of the chapter on the gastro intestinal diseases are discussed measures for the treatment of dyspepsia, they nearly always fail when instituted for the control of the dyspepsia accompanying cirrhosis of the liver, the reason being that such dyspepsias are due to coagulation throughout the gastro intestinal tract and that they are relieved only when the coagulation is made to decrease, i.e., when the cirrhotic process is abated or arrested.

Anemia—See the discussion of anemias of this type in the chapter on the anemias. Transfusion is often resorted to in cirrhosis not only for its temporary restoration of erythrocytes but also because it replenishes to some extent the depleted supply of plasma proteins.

Itching—Sponging not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. One of the calamine lotions, or the oatmeal bath (see in Eczema), is helpful to some individuals. Sometimes sweating brings relief, either induced by applied heat or the use of pilocarpine nitrate $\frac{1}{8}$ to $\frac{1}{2}$ grain (0.006–0.012 Gm.) by mouth or hypodermically, repeated so as to maintain mild diaphoresis, in some individuals aspirin (acetylsalicylic acid) will produce as much sweating with fewer side actions. Lichtman reported, in 1936, that since his introduction, in 1931, of the use of ergotamine tartrate in cases of intractable itching, he had obtained relief in about half his 75 cases, numerous other observers have also used the drug with satisfaction. ergotamine tartrate (gynergen), 1/60 grain (0.001 Gm.), three times daily by mouth, or subcutaneously or intramuscularly once a day in a dose of 1/60 to 1/20 grain (0.001–0.003 Gm.) But one must not overlook the potential toxicity of this drug, see under Migraine. Prinzmetal (1934) used the nitrates with satisfaction, giving amyl nitrite, nitroglycerin, or erythrol tetranitrate just as in angina pectoris. In the experience of Rowntree and many others, calomel has proved the most effective agent, it is used in doses of $\frac{1}{2}$ to $\frac{1}{4}$ grain (0.015–0.03 Gm.) hourly for four doses a day (omitting the usual saline) for periods of three or four days. Sodium thiosulfate is also sometimes abortifacient when given intravenously in a dose of $7\frac{1}{2}$ to 15 grains (0.5–1 Gm.).

to be repeated as necessary. Insulin in small dosage, without accompanying dextrose, has been said to be helpful in a few cases, calcium salts may also be worth trying.

Hematemesis—For the treatment of gross hemorrhage from the stomach, see Peptic Ulcer. Checking of bleeding from esophageal varices is approached by ligation of the coronary veins of the stomach or resort to the other surgical procedures mentioned later, recently, Moersch (1940) of the Mayo Clinic, has reported the successful sclerosing injection of these varices in 1 case. Drenchhahn (1939) feels that it should be possible in each case to determine the level at which blood viscosity reaches a point at which flow through the liver is hindered and strain upon the collaterals becomes great enough to produce hemorrhage, having determined the level—in terms of hemoglobin percentage and erythrocyte count—at which the patient habitually bleeds, he submits that a venesection of several hundred cc. be performed for the following principal reasons: (a) spontaneous hemorrhage with its psychic shock is prevented, (b) the quantity of blood lost may be regulated, (c) general health is improved when the blood count is kept at a more nearly constant level, (d) the blood withdrawn can be used for transfusion. Drenchhahn reported 1 case apparently very satisfactorily handled according to these principles.

Ascites—**Paracentesis**—Soon or late all cases have to be tapped. The tapping is a procedure which it were idle to attempt to describe here since its technic can only be learned in the clinic. The indications, however, are another matter, they are well stated by Hero:

"Tapping should not be delayed so long that serious displacement of the diaphragm and excessive intra abdominal tension have occurred. Something might perhaps be said in favor of the possible usefulness of moderate effusions as promoting the development of collateral circulation by giving external support to the splanchnic circulation, but there is no doubt that too long delay of tapping is inadvisable. Some external abdominal compression should be used after paracentesis to prevent as far as possible rapid distention of the portal tributaries and reaccumulation of effusion. The operation should be performed as frequently as the reappearance of ascites in considerable amount, requires."

Diuretics—For discussion of the drugs see Congestive Heart Failure. By general consent the best of them in cirrhosis are the mercurials, but the best is none too good. Christian (1936) feels that their use at times prolongs the intervals between tapings, Hayman (1936) also believes that this may be so.

Snell (1938) warns that if good increases in the volume of urine are not obtained, diuretics should be omitted, for he says their forced administration has often led to fatal hepatic and renal insufficiency.

Surgical Treatment.—A number of short-circuiting operations to divert blood from the collateral circulation, as well as measures to establish additional connections between the portal and the general circulations have been employed with variable results. The best known of these, the Talma-Morison omentopexy, is believed by Höffner to be beneficial in only one third of the cases, which is in agreement with the opinion of Eliot and Culp. Snell (1938), and Henrikson (1936) are no more sanguine. The operation is accompanied by high immediate mortality. Splenectomy, though giving great

relief in some cases by removing a substantial hurden from the portal circulation, is also accompanied by high surgical risk and not generally productive of so excellent results as in Banti's disease

Hepatic Insufficiency.—In advanced cases in which there is very great depression of liver function, such symptoms appear as loss of memory, delirium, convulsions and coma. These manifestations of toxemia may usually be made to disappear, at least temporarily, under the administration of adequate amounts of water and carbohydrate

It has now become the almost universal practice in these cases to administer 5 to 10 per cent dextrose solution intravenously either in amounts of 1 to 3 liters during the day or steadily by the continuous drip (venoclysis) method, Hendon (1930) has given as much as 500 Gm. of dextrose daily for five successive days by the latter method. The question of the advisability of employing insulin in addition seems to me to have been settled in the negative by Soskin and Hyman (1939), who point out that in a nondiabetic patient under these circumstances the administration of insulin promotes increased storage of glycogen in the muscles, thus causing the liver to pour out more sugar and therefore further diminishing instead of replenishing its supply of glycogen

CHRONIC GALLBLADDER DISEASE

Although chronic cholecystitis and cholelithiasis are possibly separate entities, they are nevertheless so similar in their symptoms and in the therapeutic measures with which we attempt to control them, that it is legitimate and convenient to discuss the two conditions here under the common title of "chronic gallbladder disease." The victims of this disease are more often women than men and are usually near or past their fortieth year. "Female, fair, fat and forty" used to be a diagnostic alliteration of my student days—but not a very accurate one, I am convinced, for many persons who are described by none of these terms do have the disease. The symptoms are those of dyspepsia, such as acid eructations, nausea, flatulence, heart burn, and especially chilliness and a feeling of weight in the abdomen after eating. During acute exacerbations there is pain and tenderness in the gallbladder region, chilliness, malaise, more or less precordial oppression, and perhaps a slight bit of fever. There are usually frequent asymptomatic periods. A typical attack of gallstone colic—which is an acute condition not to be confused with the chronic state just described—occurs almost invariably in the middle of the night, the patient experiences excruciating pain in the upper right quadrant of the abdomen, which radiates all over the abdomen and into the back, the shoulders, and even down the arms, she sweats profusely, is usually much excited and assumes many different positions, both in and out of bed, in an attempt to put an end to the agonizing pain. Such an attack usually persists only a few hours, but it may last for several days with remissions. When palpation becomes possible, on the subsidence of pain, it will be found that the gallbladder region is exquisitely tender, usually some degree of jaundice appears also

after the paroxysm is over, or at least the urine will be bile tinged and the feces undercolored. Chronic obstructive jaundice is rare in gallbladder disease unless there is an accompanying chronic cholangitis of considerable degree. It is to be noted that "gallstone colic" may occur in cases of chronic gallbladder disease in which there are no gallstones present.

Gallstones are supposed to be formed as the result of infection of the gallbladder, stasis of bile, or alteration in the chemical composition of the bile, as yet we have very little exact information on the subject. In chronic gallbladder disease, either with or without gallstones, the pathology in and about the gallbladder varies greatly there may be a simple catarrhal inflammation with moderate swelling of the mucous membrane, or the viscus may be distended with mucopurulent material, or there may be many adhesions binding it in a distorted shape to the liver, pylorus and duodenum or it may be much thickened and contracted and show actual erosions of the mucous membrane. Gallstone colic is due to spasm of the inflamed muscular viscus, to its distention with bile, to the temporary lodgment of a stone in the cystic, hepatic, or common duct, or to spasm of the sphincter of Oddi, but the cause of the much more vague constitutional symptoms of chronic, nonparoxysmal gallbladder disease is no more definitely known than is indicated in the statement that 'the gallbladder becomes a focus of infection'. Lyon believes that not only does the gallbladder become a distributing center for what he calls 'poisoned bile,' through its lymphatic connections with the liver and pancreas, but that hepatitis and cholangitis also play a prominent part in the pathologic picture, his position is that the liver, the gallbladder and the ducts are guilty of initiating a vicious circle since they pour into the duodenum 'poisoned bile' which, being taken up by the mesenteric veins and lacteals, is conveyed throughout the body 'to exert a harmful effect on all tissues'. I do not believe that he has proved the "poisonous" nature of this bile, and do not see why one should not agree with Carlson when he says "Koch's postulates are still good science and good medicine. Has Lyon or Smithies reproduced the disease by putting the duodenal return into the duodenum of well persons or dogs?"

Gallstones were first recorded by Gentile da Foligno in the fourteenth century.

THERAPY

Dietetics, Nonsurgical Drainage and General Treatment—It seems to me that about all there is to the dietetics of chronic gallbladder disease may be simply stated: (a) Nobody having ever conclusively shown in the human that substances high in cholesterol content (brains, sweetbreads, kidneys, liver, fish roe, egg yolk are the principal ones) are really conducive to gallstone formation, there is really no reason for eliminating these substances from the diet. (b) Fats make some of the patients uncomfortable probably by increasing cholecystokinin production and thus promoting gallbladder contraction, which may give rise to discomfort if the sphincter of Oddi does not at once become patulous. (c) If fats do not cause discomfort their employment may actually be of value in stimulating drainage in the above fashion. This is probably the chief service of olive oil, given usually in a 1 teaspoonful dose one half hour before meals and before retiring.

Another method of promoting drainage is by the oral administration of magnesium sulfate which, like olive oil, relaxes the sphincters. Hurst, in

England, is well known as a stout champion of the use of the drug the patient takes the largest dose short of that which he finds upon experiment to cause looseness of the bowels—every morning the concentrated solution is drunk (it may be flavored with lactated pepsin or a small amount of the compound tincture of cardamom), and the patient then lies on his right side for a while before breakfast. Knight has been using the method in this country since 1922, and Soper since 1925, both reporting good results, the former also has some fat taken thirty minutes after the salt in order to contract the gallbladder. Lyon prefers to introduce the duodenal tube and, when its tip is in the correct location to introduce 40 to 50 cc of 33 per cent magnesium sulfate solution. In a little while, bile begins to flow out of the tube, at first it is light lemon colored (A bile), then it changes to a more viscid consistency and is golden brown or green (B bile), and then it changes again and becomes much lighter and thinner than either of the two previous specimens (C bile). The A bile is said to come from the common bile duct, B from the gallbladder, and C from the liver itself (i.e., freshly secreted bile) but there is very little proved fact to support these assumptions. Lyon cites many cases in which improvement in symptoms has followed upon single or repeated drainages with the duodenal tube, but study of his book and his subsequent publications leaves some of us rather skeptical. The enthusiasm of himself and his followers is at times almost hilarious, but they claim results in almost all the ailments to which man is heir, and they certainly do not show that the mental attitude of their patients is not tremendously affected by the atmosphere of almost religious awe with which the institution of a duodenal "drain" has come to be surrounded. It seems to me that the only significant difference between the peroral and the tube methods of 'non-surgical drainage of the gallbladder' is that in one the bile goes down and in the other it comes up, in either case it goes out.

Collins (1940) has recently stressed the point, in behalf of tube drainage, that hypertonic magnesium sulfate solution given by mouth is reduced to isotonicity and that a part of the solution is converted in the duodenum into sodium sulfate which is thought perhaps to constrict instead of relax the sphincter of Oddi—however, by no means all of the magnesium sulfate is so converted and it is not proved that sufficient does not survive to promote the "drainage" even though the ritual of the tube has not been performed. As to the possibly harmful effects of having infected bile pass out through the intestine instead of through the tube, witness Carlson: 'We are swallowing bacteria every day. There are a few bacteria that are specifically toxic in the intestine. There are a few toxins poisonous by mouth, but, so far as I know, we could eat pus, ordinary pus, and not be influenced, excepting esthetically. It is not clear, therefore, that finding bacteria or pus in the duodenal content means injurious effects from the bacteria or bile lower down.'

Bile salts, perhaps best given in the form of decholin 4 to 8 grains (0.25 to 0.5 Gm) two or three times daily, stimulate the production of bile, but since no one has proved that in gallbladder disease the liver usually fails to secrete properly, I cannot understand the rationale of the routine employment of bile salts. Ivy and Berman (1939) seem to look upon the two chief indications as (a) to "flush" the biliary passages with a copious flow of bile of low viscosity in the hope of counteracting a tendency toward stasis, (b) instances in which there is sufficient hepatitis to diminish bile salt syn-

thesis but not to prevent bile pigment excretion, i.e., bile salt deficiency in the presence of pigmented feces. The evidence for the very frequent occurrence of either of these indications is not clear to me in the literature. However, bile salts are very plentifully employed in practice, therefore I must be wrong.

Methenamine (urotropin) is not a biliary antiseptic. Burnham long ago laid that ghost, nor did Tsu's (1937) recent reinvestigation supply it with any new stalking power, so far as I am able to judge.

Spa treatment is often of value in cases of chronic gallbladder disease, not so much because of the mineral content of the waters as because of the fact that a large quantity of water *per se* is drunk, and also by reason of the really tremendous psychic readjustment which takes place in many people when they visit a pleasant health resort.

Gallstone Colic—In a very mild attack, a simple enema of warm physiologic saline, or of 1 per cent sodium bicarbonate, will often bring relief, a dose or two of a carminative (for prescription see Index) nicely supplements this treatment. Hot fomentations, as described under Pneumonia, should be applied to the gallbladder region. In a severe attack, none of these measures is of any avail, morphine, or dilaudid, will usually bring relief. According to the work of Macht, who has shown that papaverine, narcotine, and narceine are more potent than morphine in causing inhibition of gallbladder contractions, pantopon would be indicated instead of morphine or dilaudid in gallstone colic, since this drug contains the isolated alkaloids of opium in their natural proportions, however, it is not my impression that clinical experience has supported this viewpoint. The average dose of pantopon is $\frac{1}{2}$ to $\frac{3}{4}$ grain (0.02–0.03 Gm.), by mouth or hypodermically. A dose of $\frac{1}{16}$ grain (0.0006 Gm.) of atropine sulfate is usually combined with the first dose of any of the opiates, but it would probably be better to give it in a larger dose in order to relax the pylorospasm which is often an associated phenomenon. Walters *et al.* (1937) did not find that atropine, even in large dosage, was able to overcome the contraction of the sphincter of Oddi caused by morphine. In a small series of cases, Bauer *et al.* (1931), at the Massachusetts General Hospital, caused prompt relief by slowly injecting intravenously 20 cc. of a sterile 5 per cent solution of calcium chloride. I understand that the method is still in use and productive of good results provided there is not too much associated inflammatory disease at the time of the attack. Beware, proceed calmly here, even though the patient is writhing in pain, see Lead Poisoning for the reasons. In a small series of cases, McGowan *et al.* (1936) obtained relief through the use of nitrites as in angina pectoris, Walters *et al.* (1937), Best and Hicken (1938), Volm and O'Brien (1939), and McGowan and Henderson (1940) have also reported satisfaction with these drugs in small series of cases in which sphincter spasm appeared to be the cause of the pain. In rare cases, light or even relatively deep general anesthesia must be instituted in order to bring release from the agony. Return to full diet after the attacks must be very gradual.

Surgery—Medical measures, though they will carry a patient through an attack of colic, will not cure gallstones, that is to say, we know of nothing that will effect the dissolution of the stones, and so long as they remain these attacks are likely to recur. There does not seem to be general agreement among surgeons as to the advisability of operating during the attack, at least the emergency is not considered at all comparable to that of acute

appendicitis, and perhaps most surgeons think that delay of several days is of advantage in allowing time in which to improve the patient's general condition. Indeed, many medical men feel there is no evidence that delay occasions any serious threat to the welfare of the patient whose colic has been mild, and that recurrence may not take place for a very long time. However, when a stone has become impacted in the common duct, or when the attacks are frequent and the general health failing the consensus is that operation is certainly indicated. Common duct operations are the most dangerous—a fact upon which many surgeons base their plea for operation in any case in which gallstones have been diagnosed with certainty, since this will in most instances save the patient the risk of a possible operation for stone impacted in the duct. Miller's (1932) study of the association of cardiac pain with disease of the gallbladder is of interest in that it has caused a number of surgeons to recall instances in which 'heart trouble' disappeared after cholecystectomy.

DISEASES OF THE RESPIRATORY TRACT

DISEASES OF THE RESPIRATORY TRACT

Sydenstricker, of the United States Public Health Service, has pointed out that the use of death rates as an index of the prevalence of disease has become so universal that the problems and aims of public health are set forth almost entirely in lethal terms when statistics are used. Valuable statistics these, but their use unfortunately sometimes serves to obscure the fact that there is still a tremendous amount of "ill health" in the world, even though people so fortunate as to dwell in civilized lands do not die so young as they did a few decades ago. What doctor of any experience at all needs to be told that the ailments of most individuals are seldom dangerously severe, though they are nevertheless of very great importance both to the individual and the community? Among these important affections that make people simply "sick," acute and chronic bronchitis and emphysema and frank bronchiectasis (implying as I intend, that many cases of "chronic bronchitis" are really unrecognized bronchiectasis) hold a prominent place, indeed, together with the common cold in its various stages, they occupy the most important place, for it is certain that an upper respiratory infection is the diagnosis most often made in home visits in Great Britain and the United States—doubtless this is also the case in the other North Temperate countries as well. The winter cough, often becoming a year round cough, of late middle aged and elderly people, coupled with shortness of breath and cyanosis on exertion, i. e., that which we call chronic bronchitis and emphysema, may be just that, but the wise practitioner makes a careful search for a possible underlying cardiovascular disease, aortic aneurysm, bronchiectasis (see below), asthma, gout, syphilis, or some other debilitating disease. The treatment of these twin afflictions has advanced hardly at all since the days of our great-grandfathers. Moderation in all things, the quiet and regular life with shunning of all vigorous pursuits, a residence in the South during the winter—all of these measures are quite helpful to the few for whom they are possible. The treatment of cough is described under Common Cold.

BRONCHIECTASIS

Increasingly in recent years the profession has become aware of the large number of cases of bronchiectasis which occur independently of any association with pulmonary tuberculosis, pneumoconiosis or tumor of the lung, indeed, one finds some qualified observers who feel that the condition is about as common as tuberculosis. Case distribution is about equal at all ages, according to Chapman and Anderson (1938), but most cases seem to begin in the first and second decades with the onset rate diminishing rapidly into old age. The patient with this type of bronchial dilatation is more

or less chronically ill in appearance, is dyspneic on exertion, has clubbed fingers, has fever at intervals, coughs a great deal, and usually but not invariably expectorates a great deal, the sputum is often but not always very foul, and often but not always it stratifies into three layers on standing. Pulmonary hemorrhages are of frequent occurrence. It is generally considered that the classification of the dilatations into the cylindrical, saccular and varicose (beaded) forms comprises the vast majority of cases, other classifications, such as that of Chapman and McCullough (1941), are far too complex for presentation here. It seems that bronchiectasis may involve part of one lobe, the whole of one lobe or part or all of many lobes, but apparently after it is once established it seldom spreads from one lobe to another. But infection may spread from the bronchial walls to involve the peribronchial and pulmonary tissues, giving rise to suppuration and foul sputum. With regard to etiology the consensus is that the condition is a sequel of pulmonary infections such as pneumonia, empyema, abscess, tracheo-bronchitis, or influenza, or of chronic sinus disease. Watson and Kibler (1938) believe that there is a definite chain of events in most cases: first, an allergic bronchitis, second atelectasis and finally, bronchiectasis. The only extensive prognostic study I have seen in which no case that had not been followed for at least five years was included is that of Bradshaw *et al* (1941). 34.5 per cent of their 171 patients died of bronchiectasis or its complications, the average duration of life in the dead patients from the onset of symptoms being 13.5 years. But this is a serious disease not only because of its high, if long postponed mortality, but also because by its very nature it handicaps its victim psychically, socially, and economically, as well as physically. The differential diagnosis is often very difficult and usually rests finally upon the injection of iodized oil into the bronchial tree with subsequent roentgen study.

THERAPY

General Medical Treatment—The general hygienic treatment of tuberculosis is profitably employed in advanced cases of bronchiectasis, *i.e.*, the patient should rest a great deal, if not entirely confined to bed, and should be given a well balanced nutritious diet and as much spiritual encouragement as possible.

Postural Drainage—Patients do not have to be encouraged to employ this measure for they have often found the most suitable posture for drainage of their own accord. King (1939) says that with lower lobe involvement the best position is on the face with the shoulders lower than the hips, some patients lie across the bed with the shoulders near the floor, others kneel in a chair with the hands on the floor. Lying on the back with the foot of the bed moderately elevated seems to serve best in cases with the right middle lobe or lingula of the left upper lobe involved, in the rare upper lobe cases the sitting posture is said to be the most satisfactory, and if the disease is in the lower part of the upper lobe the position of choice is lying on the unaffected side. In some hospitals postural drainage beds are available nowadays.

Lipiodol Injections—The oil is introduced either through the bronchoscope or by injection from a syringe, or it is inhaled from the mouth. All of these are special techniques which of course cannot be learned from the pages of a book. Opinion varies as to the action of the oil: some say it dilutes the sputum and allows it to be raised with greater ease, others that it displaces

the sputum from the bronchiectatic cavities, and others that it merely reduces irritation by coating the bronchial walls. Some patients are helped, others are not, it does not seem possible to discover in the literature what the proportions are.

Bronchoscopic Drainage—Occasionally this procedure is resorted to. It seems a drastic measure, but King says patients are often aided enough to insist on continuation of the treatments.

Collapse Therapy—It is the consensus that these measures, so useful in pulmonary tuberculosis, are seldom helpful in bronchiectasis and that their employment may preclude subsequent lobectomy.

Abdominal Belt—Alexander and Kountz (1934), Gordon (1934), and Meakins and Christie (1934) have each described a special type of abdominal binder the wearing of which is said often to give relief, some patients, however, cannot tolerate these belts even though they give them partial respiratory relief.

X-ray Therapy—Berck and Harris (1937), at Mount Sinai Hospital in New York, treated a small group of chronic cases with moderately large doses of roentgen ray with a considerable degree of improvement in a fair proportion of the cases. Fink (1941) says that they have concluded at the University of Minnesota Hospitals that little was gained by roentgen therapy usually, though it might be worth trying in selected cases.

Drugs—Of course the sulfonamides have been tried but one does not hear that the results have been brilliant. It seems that neoarsphenamine may be of value in occasional instances, particularly if fusospirochetal organisms are present and the sputum is foul, both King (1939) and Singer (1939) mention the drug. Creosote is also used to overcome the foul odor, in some such prescription as the following:

R ₁ Creosote (beechwood)	gtt vj	0 4
Glycerin	3j	32 0
Peppermint water (or plain water) to make	3iij	96 0
Label: Two teaspoonfuls every two to four hours, well diluted		

This prescription contains a small amount of the drug, but when it is finished the next should contain double this quantity, i.e., 12 drops. The creosote should then gradually be increased to the point of tolerance as marked by anorexia or other gastro intestinal disturbances. The dose is then reduced to the amount the patient well tolerates and is best given directly after meals. When the larger doses are being given the urine should be frequently examined for albumin, or for signs of phenol poisoning, and if the kidneys are at all disturbed the creosote should be at once stopped. Creosote carbonate is sometimes substituted for creosote in doses twice or thrice the size. Creosote is sometimes vaporized by igniting it and the patient, breathing the fumes, in a closed room, coughs violently and expectorates profusely, King quotes authors who have found these "baths" useful when given two or three times daily.

Climate—Climatic change sometimes benefits the patient, and it is not always the warm dry climate which is best, for some individuals do well at the seashore or in the mountains.

Desensitization—Watson and Kibler (1938) report considerable improvement in some of their cases in which desensitization therapy was employed.

most common sensitizations were to feathers, pollens, orris root, house dust and wool, but there were a few cases in which foods were said to have been the most important factor

Lobectomy—The technic of this operation has improved so much that many thoracic surgeons are now hopeful of some day being able to offer complete relief in this way to the majority of patients. It is considered that in skilled hands in properly selected cases the mortality should be very low. Clagett (1942) has recently made a plea for operation on the patients as young and as early as possible.

ABSCESS OF THE LUNG

Abscess of the lung may follow a severe bruise of the chest wall or a penetrating wound of the lung, or it may occur during the course of chronic pulmonary tuberculosis, or it may occur as a sequela of pneumonia, especially the influenzal type of pneumonia. Its occurrence following operations in the mouth and throat of adults is notorious, particularly when general anesthesia has been employed. Whatever the cause, the cardinal symptoms and signs are cough and explosive expectoration, localized chest pain, foul breath and sputum, elastic tissue in the sputum, dullness on percussion over a circumscribed area, and positive x ray findings. Sometimes the symptoms of sepsis, such as intermittent fever, sweats, high leukocytosis, etc., are present. However, diagnosis is by no means always easy and not infrequently is made only at the autopsy table.

THERAPY

The so-called conservative therapy of lung abscess is about the same as that of bronchiectasis, i.e., general building up treatment, postural drainage, bronchoscopic drainage, arsenicals or the new sulfonamides, and a miscellany of other drugs, measures and procedures. Its record is not good. The essence of this type of treatment, if I understand it, has been to try everything possible in order to avoid surgery because an even larger number of patients succumb to surgical than to the above listed medical measures. Now, however, the surgeons are showing that this "conservative" attitude has been all wrong, for Neuhof and Touroff (1940), and Overholt and Rumel (1941), by treating lung abscess as a surgical problem from the onset and instituting immediate and early drainage, are able to show results never before attained. Overholt and Rumel, for example, show that external drainage of complicated lung abscess has an operative mortality of 52 per cent and a cure rate of only 26 per cent, while external drainage of simple lung abscess has an operative mortality of 6 per cent with a cure rate of 94 per cent. Since most simple lung abscesses are of short duration and most complicated lung abscesses are of longer duration, it becomes obvious that lung abscess is best considered as primarily a surgical condition in which early operation is indicated.

PLEURISY

Pleurisy, which is usually abrupt in onset sometimes with pronounced chill, often follows exposure to cold or it may be a sequela of some other respiratory affection, in a few cases neither antecedent condition appears in the history. There is a stabbing pain in the side which is aggravated by breathing and changes in posture usually a hacking cough which also aggravates the pain increased respiration several degrees of fever leukocytosis, and a number of typical physical signs the chief of which is a leathery friction rub. In some cases the pain is referred to the abdominal region which makes differential diagnosis somewhat difficult also in some instances the patient never at any time experiences any pain. Latterly an interesting theory has arisen which explains the pain in pleurisy as due not to friction of the opposing inflamed parietal and visceral membranes as is the time honored belief, but solely to tension of the inflamed parietal layer which is stretched during respiration.

Pleurisy with effusion differs very little in its onset from the dry variety but when the inflamed pleural surfaces begin to be separated by the fluid the pain disappears and dyspnea develops, it is not in order in this book to describe the numerous other physical diagnostic signs of effusion. Occasionally a patient feels very little subjective distress whatever.

The immediate prognosis in both forms of pleurisy is good. A dry case usually clears up gradually in two to three weeks a case with effusion is often protracted much beyond this period. However the fact that an attack of pleurisy is looked upon as presumptive evidence that the individual who suffers it is tuberculous makes the disease of much more serious import. Some physicians of vast experience maintain that all cases of pleurisy are tuberculous, others hold that all cases not accompanied by the signs of a known infection such as typhoid are tuberculous others are doubtful regarding dry cases (only 4 of Fulton and Hahn's [1931] 40 cases developed pulmonary tuberculosis during an average period of observation of seven years) but believe all cases with effusion to be of tuberculous origin (though Trudeau 1939 could find x-ray evidence of the disease in only 20 of 83 cases) while there are those who lacking positive evidence of tuberculosis in a first attack always make a diagnosis of tuberculosis in any patient who has pleurisy twice whether with or without effusion.

Boerhaave (1668-1738) was the first to show that pleurisy is an affection of the pleura alone.

THERAPY

The patient with dry pleurisy should be kept at rest—indeed he will impose the most absolute immobility upon himself, usually lying on the affected side with the shoulder depressed and the arm stretched along the body. Compresses are hardly worth using for relief of the pain. The best measure is the application of adhesive plaster strips (2 inch width) with the chest in the expiratory position. They should pass from the vertebral column to the midline in front at right angles to the column not starting with the ribs begin below and let each strip slightly overlap its predecessor. The cough does not usually require special treatment if the affected side is immobilized in this way. In severe cases 1 grain (0.065 Gm.) of codeine sulfate or if necessary $\frac{1}{2}$ grain (0.015 Gm.) of morphine sulfate or $\frac{1}{2}$ grain (0.002

Gm) of dilaudid hydrochloride should not be withheld in the beginning. A number of physicians believe that calcium and parathyroid extract are effective at times in preventing effusion or promoting its resorption, for methods of administering these drugs see Lead Poisoning.

Shaw (1935) has interestingly pointed out the danger of inducing basal atelectasis, especially in elderly individuals, through partial immobilization by strapping or as a result of respiratory depression consequent upon the use of opiates. In two instances in which atelectatic pneumonia had already developed, he induced shallow pneumothorax with 200 to 250 cc. of air, and obtained almost immediate relief and the recovery of both patients, in whom it had been felt that the prognosis was extremely grave at the time of making the injections. He believes that the usual objections to artificial pneumothorax—risk of secondary pleural infection of causing or increasing myocardial distress of pleural shock and air embolism—are bogies with a very infrequent incidence.

When fluid appears in sufficient quantities to aggravate the condition of the patient it should be removed by paracentesis. The indications for, and the technic of, this procedure are to be learned in an apprenticeship upon the wards and not from the pages of a book. Attempt should not be made to remove the effusion by diuresis or catharsis for the fluid cannot return with sufficient rapidity through the inflamed serous membrane to make up for the loss of water by way of the kidney or bowel, the patient will thus only be weakened to no purpose. Blisters are also of little or no value.

The necessity for looking upon an individual who has once had an attack of pleurisy as a tuberculosis suspect is of the utmost importance since by accepting such an attack as a sign from the gods that a readjustment of the mode of life is in order, we may sometimes entirely prevent the appearance of a frank pulmonary tuberculosis.

Trudeau (1939) finds the prognosis excellent in cases with effusion whether they have negative doubtful or extremely slight apical pulmonary findings by x ray—if these patients receive at least four months of sanatorium care.

LARYNGITIS

Acute laryngitis appears rather suddenly with a dryness and tickling in the throat and some pain on swallowing, oftentimes there is tenderness to pressure made upon the protruding portions of the voice box in the neck. The voice becomes husky and speaking is not only painful but is also provocative of extreme weariness. Cough may not be present in the beginning but it usually develops quite soon and serves to eliminate considerable amounts of mucus. Not infrequently the voice is completely lost during the few days' duration of the attack.

Laryngitis usually follows exposure to sudden changes of temperature sudden climatic changes, inhalation of irritating materials or excessive or faulty use of the voice. Occasionally the condition becomes chronic, in these cases there is nearly always a discoverable source of chronic infection in the nasopharynx.

THERAPY

Rest of the body, and especially rest of the voice, are the most important elements of treatment. Complete silence for forty-eight hours works wonders in these cases, but is practically never possible of enforcement.

Confinement to a room in which the temperature is maintained at an even level and the air moist is helpful. Some patients like to apply cold compresses to the throat. The use of a steamy inhalation mixture, such as is described under the treatment of Common Cold, is soothing. Gleason said that the taking of 10 drops of dilute nitric acid in a glass of water every two hours, is often helpful in the aphonia of singers and speakers, a statement which is fully corroborated by the experience of many of the older practitioners.

The use of drugs to control the cough is doubtfully advisable since it serves a benign purpose, when it becomes too severe. However the preparations described under the treatment of Common Cold should be considered.

Oftentimes reeducation in the use of the voice is necessary for those who are suddenly thrust into a public speaking career.

NEPHRITIS AND NEPHROSIS

NEPHRITIS AND NEPHROSIS

Acute diffuse glomerular nephritis usually makes its appearance, abruptly or insidiously, in children or young adults several days or weeks after apparent recovery from an upper respiratory infection or from one of the acute streptococcic infections, such as tonsillitis, scarlet fever, rheumatic fever or erysipelas. Many observers now believe that the attack is the expression in the kidney of a widely diffused vascular inflammation, which may be allergic in nature. Cases occurring during a subacute bacterial endocarditis are usually looked upon as "focal" rather than "diffuse" the differentiation being made on the smaller number of glomeruli found to have been involved in the rare specimens that come to autopsy, plus the absence of hypertension and edema. In the common or diffuse form there are present both edema and hypertension, but the former is rarely of the marked pitting sort seen in nephrosis, and the hypertension is usually not inordinately high and very rarely may not be present at all. There is more or less albumin in the urine but the characteristic feature of these cases, in addition to the hypertension, is the presence of red blood cells and red cell casts often enough to cause the urine, which is diminished in amount, to have a smoky brown color.

Ordinarily the acute death rate may be reckoned at 5 to 10 or 12 per cent. The prognosis as regards ultimate recovery without permanent sequelae, though now admitted to be better than formerly believed, varies considerably. Cass (1930), studying 88 cases in England, found that the condition ultimately became a chronic one in 82.0 per cent of those who had not died in the acute attack, Snoke's (1930) figure for a large series of cases in San Francisco was 47.2 per cent, while for a series in Rochester, N. Y., it was 13.7 per cent, here in Milwaukee, Murphy and Peters (1942) report the following outcome in 205 cases studied during a ten year period: 12.6 per cent died during the acute stage, 17.0 per cent were discharged recovered but were not reexamined, 34.1 per cent recovered and were found healed upon reexamination, 9.2 per cent were found latent upon reexamination, 26.8 per cent became chronic nephritics. Most clinicians are now in agreement that patients who experience the most turbulent onset often have the best outlook for complete recovery. Cases advancing toward chronicity frequently develop subacute exacerbations during which there is some elevation of temperature and the urine is clouded with blood and casts, but as the glomeruli are gradually destroyed during months and years the urine contains less blood and fewer erythrocytic casts, and finally nitrogen retention, manifested by rise in blood urea and creatinine, makes its appearance foretelling uremic termination—though it has been remarked that in all *fatal* cases of chronic nephritis characterized by severe nitrogen retention there is an acidosis severe enough in itself to be the actual cause of death. It has also come to be increasingly recognized in recent years that severe anemia is an accompaniment of decreasing renal efficiency, though it may also appear early in the acute cases, considerable disturbances in calcium metabolism are also sometimes seen. Lipemia often very marked, tends to decrease in the

terminal stages of the disease and the plasma lipid content may fall below normal just before death

The striking characteristics of *tubular (degenerative) nephritis* which distinguish it in its *pure* form from the glomerular type, are *hyaline*, waxy and fatty casts but no blood or blood casts in the urine, marked and persistent edema, and albuminuria without *hypertension* or *nitrogen retention*. This type may also appear acutely in children in the course of streptococcal or other blood stream invasions, or as a mild form complicating Asiatic cholera, diphtheria, malaria, syphilis, typhus, yellow fever and possibly other infectious diseases. It is the nephritis sometimes caused by mercury and the arsenicals, also the nephritis seen in the late toxemia of pregnancy. If, in addition, there is observed an increased blood cholesterol, refractile globular bodies in the urine, a low metabolic rate, low serum protein with a marked disturbance in the ratio of serum albumin to serum globulin, and a tendency toward a protracted course with relatively frequent complete recoveries or death from intercurrent infection without the appearance of signs of severe inflammatory renal disturbance—in these cases the diagnosis of *lipoid nephrosis* is made, which is considered by some observers to be a rare entity not directly related to inflammatory nephritis.

The type of kidney disease known as *arteriosclerotic nephritis* is only one element in the cardiovascular-renal syndrome, which begins with "essential" hypertension, progresses to arteriolar disease of the body as a whole and not solely of the kidneys, and ends often in cardiac or apoplectic death before kidney complications of a serious nature have appeared. The urine is much increased in amount and low in specific gravity and contains often only a small amount of albumin and a few hyaline casts. Edema is not a usual feature of the pure form, but ultimately uremia appears in association with the slowly increasing nitrogen retention. More rapidly progressive cases are designated "malignant."

So far as is yet known, the first description of kidney disease was that of Aetius (c. 300 A. D.), who is said to have found at autopsy that certain cases of dropsy were associated with hardening of the kidneys. Rhazes (860-932 A. D.), the great Arabian clinician, probably also recognized the entity but no further advance toward its understanding was made until Avicenna, that "convivial Omani spirit" at the court of Bagdad, noted that in dropsy the urine was considerably altered. Then Saliceto, in the middle of the thirteenth century, provided the classical description of edema associated with contracted kidney, and Malpighi (1628-1694), aided by the great discoveries of Harvey (1578-1657), established the function of the capillaries. Thus were laid the foundations upon which Richard Bright (1780-1858) was able to erect his anatomico-pathologic-clinical classification a hundred years ago.

THERAPY OF ACUTE NEPHRITIS

Rest—It is the consensus of course that the patient should be in bed and at complete rest during the early stages, but there is difference of opinion regarding how long this absolute rest should be imposed. Page (1940), it seems to me, is for keeping the patient in bed as long as this may be easily done, but Goldring (1941) believes that he should be allowed out of bed when the hypertension and edema have disappeared even if there are still

urinary abnormalities, for he makes the point that nitrogen and some blood may persist in the urine for three to six months longer even in those who ultimately recover. Murphy and Rastetter (1938) seem to feel that the persistence of hypertension and urinary and other laboratory findings after three months mark the transition into chronicity and that nothing is gained in keeping the patient in bed any longer.

Diet and Fluids—There has been argument in the profession since time out of mind regarding the type of diet to be employed in acute glomerular nephritis, with a good deal of wobbling in more recent times as bits of experimental evidence from small animal observation has been introduced to bolster one side or the other. As a matter of fact if anyone has yet proved the harmfulness of allowing the patient as much of a mixed diet, including proteins as he wants to take (which is usually not much in the beginning), I can only say that I have not seen the report. Fluids, too, may be given in such quantities as the patient desires. Obviously, sodium chloride should be restricted in the presence of edema. Excessive acidity of the urine may be corrected by the use of fruit juices or perhaps 15 grains (1.0 Gm.) of potassium citrate. Certainly enough time has passed for the "hunger thirst" cure of Volhard to have justified itself unequivocally but it has failed to do so. Murphy and Pietraszewski (1940), here in Milwaukee, compared high protein and relatively low protein diets and found that the patients did as well on the one as the other but were more satisfied on the high protein diet, incidentally, the high protein was an acid ash diet and the other an alkaline ash diet so this study provided a comparison of these factors also. Goldring (1941) says that their practice at Bellevue Hospital is to allow the patient to take the regular ward diet, only restricting sodium, and he says their statistical results are as good as those obtained under strict regimens. During any extended period when the patient is not taking a full diet supplementary vitamins should be given.

Edema—It is impossible in the present state of our knowledge to direct any measures toward the relief of the edema of acute glomerular nephritis since it is due to increased capillary permeability resulting from bacterial toxin injury. Diuretics are not indicated but salt restriction is of course advisable since the more sodium in the tissues the more water they can hold. The edema of acute-tubular (degenerative) nephritis, with reduction in plasma proteins requires to be handled in principle as the edema of chronic nephritis (see below).

Nonuremic Convulsions—This type of convulsion, of rather frequent occurrence in children, is characterized by the premonitory symptoms of sudden violent headache and visual disturbances, central vomiting, and a rapid rise in blood pressure, and is often followed by coma. Kernig and a Babinski sign and occasionally transient paralytic symptoms. The syndrome, not being due to the retention of nitrogenous products and hence not being true uremia, is considered to result from cerebral edema and angiospasm, it is definitely relievable by depleting measures. Magnesium sulfate is given in large doses—1 to 2 ounces (30–60 cc.) of a 50 per cent solution by mouth every four hours. If this method of administration does not check the cerebral symptoms and reduce the blood pressure the drug is injected intramuscularly. Usually 0.2, occasionally 0.4 cc., of a 25 per cent solution per kilogram (2.2 pounds) of body weight is the dose, the effects are usually seen in fifteen to

thirty minutes, but failing, the injection can be relatively safely repeated after two or three hours. Blackfan abandoned the intravenous route after finding the intramuscular just as satisfactory, but Plotz *et al* (1937), confirming Blackfan's favorable use of the drug, use it by either route, intravenously the same dosage may be employed as is used intramuscularly. Goldring (1941) also uses it intravenously. Alarming toxic symptoms rarely follow the use of magnesium sulfate parenterally, but it is well to be prepared to combat respiratory depression by the slow intravenous injection of a few cubic centimeters of 25 per cent calcium chloride solution. Hypertonic dextrose may be given intravenously instead of magnesium sulfate, 25 to 100 cc of 50 per cent solution is most often used. An objectionable feature of this use of dextrose is that it frequently induces a high secondary rise in cerebrospinal fluid pressure. Both Page (1940) and Lueth (1941) speak favorably of the intravenous administration of 50 per cent sucrose solution, giving from 50 to 250 cc but injecting very slowly if cardiac failure is impending. In rare instances sucrose seems capable of causing tubular degeneration, but the effect is only transient and it would seem from the work of Lindberg *et al* (1939) is not likely to alter renal function. Venesection may be of value, spinal puncture is definitely of aid if coma supervenes—but Goldring warns that the fluid must not be permitted to run out fast.

Hypertension—In most instances the hypertension *per se* is transient and does not call for treatment directed specifically toward its relief, which is fortunate since we know so little of its causation. In some instances magnesium sulfate parenterally, as in treatment of convulsions (see above) relieves hypertension. Rubin and Rapoport (1941) feel that probably the effect is due to a relaxation of the generalized vasospasm through local action on the smooth muscles of the blood vessels.

Heart Failure—It is the general impression that myocardial involvement is rare in acute glomerular nephritis, but Whitchell *et al* (1939) found the signs of circulatory insufficiency very frequently in the moderately severe and usually in the very severe cases among their 138 patients. This type of congestive heart failure responds to digitalis or ouabain in the usual way (see Index for methods). Goldring (1941) feels that the drastic treatment (ouabain intravenously) is usually called for.

Anuria—Anuria is not a common occurrence, which is fortunate for it is usually accompanied by uremia and is likely to be fatal. Page's (1940) recommendations for treatment may be outlined as follows: (a) Catheterize to be sure there is no obstruction. (b) Give 50 per cent dextrose intravenously. (c) Try a hot bath lasting thirty minutes or more, simultaneously administering 400 to 500 cc of fruit juice. (d) If there is acidosis, give sodium bicarbonate by vein. (e) If all these measures fail and little or no urine has been passed for three days decapsulation of the kidney should be tried. Murphy (1936) increases the fluid intake to 2000 or even 3000 cc per day, regardless of the presence of edema or the danger of inducing it. Goldring (1941) is very skeptical of the value of any efforts to get the urine flowing again, he points out particularly that if the cause of anuria is a deficient blood flow through the glomeruli, as it probably is, it is difficult to see how the administration of hypertonic solutions of sucrose or dextrose would correct the functional disturbance. It is significant, too, that decapsulation is performed much less frequently now than a decade or two ago.

Uremia—See under the same heading in the therapy of Terminal Nephritis. In acute glomerular nephritis the symptoms are often alarming but the condition is apparently not of serious moment since as many complete recoveries seem to occur in those who developed an extremely high non protein nitrogen as in those who did not.

Treatment of Infections—Williams, Longcope and Janeway (1942) have used sulfanilamide in 42 patients in the acute stage of nephritis, nearly all of them being patients from whom beta hemolytic streptococci had been cultured from some focus. The results indicated that under the drug the foci of infection cleared up more rapidly, the signs of renal damage disappeared more rapidly, exacerbations of the nephritis following tonsillectomy occurred less frequently, the duration of edema and hypertension was reduced, and the proportion of clinical recoveries was greater (74.3 per cent in the 39 patients followed for at least two years). It will be of great interest to see if such results can be generally obtained. Aside from the fact that diminished renal function enjoins caution, the nephritis itself does not contraindicate the use of sulfonamides.

Goldring (1941) undoubtedly expresses the consensus when he says that one should wait four to six months before removing suspected foci of infection even if they are obviously purulent, early removal invites recurrence of the nephritis.

THERAPY OF CHRONIC NEPHRITIS (AND NEPHROSIS)

EDEMA

High Protein Diet—The chief surviving hypotheses in explanation of albuminuria are the two which follow. First, that functional or actual retrogressive changes in the glomerular capillaries permit the passage of albumin through this filter which normally holds it back, many observers have embraced this viewpoint. Second, that there occurs a general metabolic disturbance of such nature that there is a shift in the plasma proteins toward the coarser globulin fraction, albuminuria then resulting when the kidneys excrete this foreign "denatured" protein in a quite physiologic way and without any increase in their permeability, there is much disagreement regarding this conception at present. Fortunately, in practical therapeutics it does not really matter which of the "explanations" is the correct one, for the albumin is there in the urine regardless of how it arrived, and the patient is likewise often edematous. This association of albuminuria with edema is rather well understood nowadays when the total protein of the plasma falls as a result of albuminuria, the ratio of albumin to globulin in the blood is reversed, the proportion of globulin to albumin becoming greater, however, the large globulin molecule exerting a lower osmotic pressure than did the smaller albumin molecule which it replaces, the total osmotic pressure within the vessels is lessened, and fluids pass out into, and remain in, the tissue spaces. This comprises the rationale of the high protein diets of today. The actual computation of diets (food value tables in Diabetes) can be based usually on the needs of a normal healthy individual of the patient's age, height and weight, though in frequent instances it may be necessary for a time to exceed the normal daily amounts of protein per kilogram body weight. However, the optimal amount for adults seems to be between 70 and 100 Gm, for above this loss of appetite usually occurs, in children the rate

of 32 Gm per kilogram (22 pounds) of body weight seems optimal, which is also just about the amount required for proper nutrition and growth. The sample menus offered in Table 19 contain usually adequate amounts of protein, as there indicated, it should be preferably given in the form of foods with high biological value, such as meat (there are no differences between red and white meat), milk, cheese, fish and eggs. As protein is deposited in the tissues it may increase the edema for a while until the slowly rising serum proteins (a process which may require several months) draw it out again and diuresis begins. There is no contraindication to the usual allowances of carbohydrates and fats. In many instances it is probably advisable to add supplementary vitamins. Bruger *et al* (1939) find that alcohol in moderate amounts rarely augments proteinuria and sometimes induces moderate diuresis even in the presence of considerable impairment of renal function, in spite of these observations, however, I imagine most men will continue to feel justified in greatly restricting the use of alcohol in their patients.

Water, Salt, Acid and Base Allowances—As above stated, edema results from the loss of proteins from the blood in a patient with albuminuria, but this is not the sole explanation for the water imbalance since it has been amply demonstrated that in renal edema a part of the water logging is due to a retention of chlorides. Whether this retention is due to inability of the damaged kidneys to excrete these salts, or whether they are not excreted simply because they are held by the extrarenal tissues, is still a moot point. At any rate, sodium chloride when administered is retained and edema increases if the nephritic state is at all severe or advanced. An absolutely salt free diet is certainly not advisable for the following reasons: (a) such a diet is woefully unpalatable and causes nausea and vomiting, headache and legache, and a host of other symptoms, (b) moderate reduction is easier and in the end more effective because it can be continued for a long period, and (c) the substitution of other chlorides is practicable to a limited extent.

The average daily salt ration in America is about 10 Gm, water intake probably 2000 cc. The salt can be considerably reduced without difficulty since most of it derives from its addition to foods during preparation, most raw foods being salt poor. The principal exceptions that are likely to be included in the average dietary are milk, butter, cheese, preserved meats, fish and breads. Simpson writes: "In a normal diet of an average person which includes these latter articles the salt intake, exclusive of salt as a condiment, will not exceed 3 Gm daily. The unpalatability of a salt poor diet can be overcome, partly, by using such highly flavored substances as pepper, mustard, vinegar, lemon juice, spices, garlic, onion, etc. The rather commonly held opinion that such condiments and foods are harmful to kidney structure is not supported by experimental work." Briefly, allowing any foods desired but forbidding the use of salt either in kitchen or dining room, means permitting 3 Gm, or perhaps slightly less, daily, this may be raised by actual additions of salt, lowered by omitting milk, salted butter or any other of the worst offending articles.

Since it is the sodium and not the chlorine retention which is of importance in edema the practice has arisen in recent years of substituting other chlorides for sodium chloride: ammonium chloride in amounts of 5 to 15 Gm daily, potassium chloride in amounts of 5 to 10 Gm daily, calcium chloride or even 100 to 200 cc daily of N/10 hydrochloric acid. Potassium chloride has

TABLE 10 — HIGH PROTEIN, LOW-SODIUM, HIGH POTASSIUM DIET WITH ACID ASH FOR USE IN EDEMA (After Barker)

Ingredients

Fruits	Butter
3 servings daily, fresh or stewed, but should include either prunes, plums, cranberries or currants once daily	Salt free, 6 squares
Vegetables	Cereal
2 large servings daily, especially beets, carrots, Brussels sprouts, yellow corn, kohlrabi lettuce, mushrooms, peas, spinach, kidney beans, parsnips	Oatmeal or wheatena, farina, puffed wheat or rice occasionally
Meat	Bread
2 servings daily	Graham bread 3 large slices or 6 small slices daily
Eggs	Rice, macaroni or spaghetti
2	1 serving daily
Milk	Potato
1 glass	1 serving
Cream	Jelly, preserves or honey
$\frac{1}{2}$ glass	2 level tablespoonfuls
	Sugar
	<i>Ad libitum</i> —at least 1 tablespoonful

Sample Menus

1	2	3
Breakfast	Breakfast	Breakfast
Stewed currants	Plums	Stewed prunes
Oatmeal	Wheatena	Farina
Two poached eggs	Scrambled eggs	Soft cooked eggs
Graham toast	Graham toast	Graham toast
Sweet butter	Sweet butter	Sweet butter
Honey	Jelly	Honey
Cream	Cream	Cream
Sugar	Sugar	Sugar
Dinner	Dinner	Dinner
Roast beef	Broiled steak	Broiled lamb chop
Mashed potatoes	Buttered macaroni	Buttered spaghetti
Buttered beets	Stewed tomatoes	Buttered spinach
Sliced peaches	Banana salad	Grapefruit cup
Graham bread	Graham bread	Graham bread
Sweet butter	Sweet butter	Sweet butter
$\frac{1}{2}$ glass milk	$\frac{1}{2}$ glass milk	$\frac{1}{2}$ glass milk
Supper	Supper	Supper
Broiled chicken	Broiled liver or sweet breads	Broiled whitefish
Buttered rice	Baked potato	Mashed potatoes
Jelly	Celery salad	Buttered Brussels sprouts
Lettuce salad	Cherries	Pineapple and nut salad
Orange cup	Graham bread	Graham bread
Graham bread	Butter	Sweet butter
Sweet butter	Jelly	Jelly
$\frac{1}{2}$ glass milk	$\frac{1}{2}$ glass milk	$\frac{1}{2}$ glass milk

Notes

All foods are to be prepared without salt and no salt is to be served with meals. Potassium chloride (from 2 to 5 Gm. in shaker) may be given as salt substitute. Spices—cinnamon, sage, paprika, pepper, cloves, nutmeg, allspice—may be used. Small servings of citrus fruits may be added after fluid volume is established. Additional vitamin D to be supplied in the form of vitamin D.

Coffee or tea, 1 cup daily

This diet is designed for the treatment of convalescent and ambulatory patients. Very ill patients are to be given the same foods but in smaller amounts.

had the greatest vogue but many individuals object to its metallic taste. Barker and Robinson (1933) have used 2 to 6 Gm daily of ammonium sulfate with good effect. Using a diet with a high acid ash, which is easily accomplished when high protein feeding is being employed, is also of diuretic value.

Ample experience has now shown that water restriction is not necessary. For even large volumes of water given without salt are excreted without difficulty, it is the restriction of sodium salts, particularly sodium chloride which is important, since retained sodium means retained water. Alkaline waters, such as some of the bottled waters from well known spas, should not be allowed for their sodium content will provoke water retention.

The accompanying table (Table 19) shows the type of dietary regimen which Barker and his associates at Northwestern University use in complying with all the requirements discussed above. Briefly, the patient is given a liberal diet which is adequate in every respect except that small supplementary vitamin additions (vitamin D, in particular, is deficient) had best be made now and then. The total amounts of specific minerals agree closely with Sherman's average of 150 American dietaries except in the inverted ratio of potassium to sodium. The diet is properly high in protein and has an acid ash. No sodium chloride is used in either kitchen or dining room, but the patient is given 5 Gm, occasionally more, of potassium chloride crystals in a salt shaker each morning, with this he salts his food and at the end of the day places the remainder in water and drinks it. No significant changes in blood sodium or potassium have been noted by those employing this type of treatment, and no ill effects have followed in patients who have been upon the regimen for several years, one of Barker's patients with pronounced nephrosis has required 10 Gm potassium chloride daily to remain edema free. Winkler *et al* (1941) consider it unlikely that the potassium ion can cause poisoning when it is given by mouth under the conditions here obtaining. They say that even the most severely damaged nephritic kidney continues to excrete potassium. This treatment does not alter the acid base balance.

Diuretics—The diuretic drugs are thoroughly discussed in Congestive Heart Failure. The ones most often used in nephrotic edema are potassium nitrate and a mercurial such as salyrgan or mercupurin (which also contains theophylline). One often hears the statement that the mercurials are contraindicated if there is renal pathology, but many leading clinicians feel that they may be used with impunity if good care is taken. Goldring (1941) says that it is their practice at Bellevue Hospital to give 1 cc of mercupurin intravenously, and if there is no diuretic effect after twenty four to thirty six hours another 2 cc, if there is then no effect no further attempt is made to use the drug. However, Tyson (1941), describing two sudden and very serious (one fatality) reactions of an apparent anaphylactic nature in her own experience and mentioning three other such instances in the literature, feels that the mercurial agents are contraindicated in nephrosis.

Acacia—In 1933, Hartmann *et al* introduced the method of injecting acacia solution intravenously to raise the colloid osmotic pressure of the blood sufficiently to prevent escape of fluid into the tissues. Further observation has shown, however, that the colloid osmotic pressure usually fails to be increased, probably because the volume of circulating blood increases and the serum constituents are diluted. But nevertheless diuresis is often induced by acacia injection and therefore a new explanation will have to be found.

since mere increase in the volume of circulating blood will not in itself result in diuresis, recently some preliminary animal experimentation has indicated that perhaps acacia directly promotes the excretion of chlorides. Acacia lost most of its early friends very quickly because of the severe though admittedly rare, reactions which sometimes accompanied its use, and the evidence that it is deposited possibly harmfully, in the bone marrow, spleen, liver, lymph nodes, lungs, kidneys, and edema fluid. But the agent has two stout champions still in Goudsmit and Binger (1940) at the Mayo Clinic, who apparently include it routinely with high protein diet and diuretic salts in their treatment of nephrotic edema, Lehnhoff and Binger (1942) have recently reported a case from the Clinic which cleared up remarkably well on the treatment.

Method—The use of potassium nitrate is begun two or three days before acacia is given and then the latter is injected slowly (forty five to seventy five minutes) intravenously in an average dose of 500 cc of a 6 per cent solution in water or 0.06 per cent sodium chloride solution. Injections are given every day or on alternate days for three or four times.

Results—Of 40 consecutive patients, 36 were relieved of their edema losing weight (edema fluid) at the rate of 1 to 3 pounds daily. Three patients who at one time responded well were not satisfactorily controlled during a relapse, though one of these responded rather promptly on a subsequent readmission.

Reactions—In approximately 10 per cent of the cases an urticarial reaction occurred and was controlled by epinephrine injection. Occasionally a patient complained of dyspnea or pain in the left side of the thorax during or shortly after an injection, injection was stopped and codeine given. Sometimes too fever occurred as after a blood transfusion. These workers recognize no contra indication to the continuance of acacia treatments except the very rare occurrence of a severe allergic reaction. They have never seen the blood pressure remain at a higher level than that which existed before the injection and have never seen renal damage result from the use of acacia. In fact, they mention instances of a lowering of the blood pressure and improvement in renal function. In their opinion the solution can also be used without fear in patients who have severe hepatic cirrhosis.

Transfusion—Whole blood transfusion is frequently resorted to when the edema is great enough to cause dyspnea. Diuresis and a considerable diminution of distress are often obtained, effects which may persist several days.

Lyophilic Serum—Aldrich and Boyle (1940) have used dried serum which they have diluted with sterile water to one fourth the volume of original serum from which the lyophilic preparation was made, 30 to 50 cc of this solution is injected intravenously once or several times at intervals of two days or more. Sometimes there is a febrile reaction. Diuresis has been initiated by these treatments in most of their small series of cases and as a rule has persisted until there was complete elimination of edema, sometimes with complete recovery from the nephrosis.

Amino Acids—Farr *et al* (1940) are experimenting with the intravenous administration of amino acids—an interesting development but one which has not as yet reached a point warranting its description here.

Thyroid Substance—Low basal metabolic rates have been recorded in a number of times in nephritis, but a reclassification of the disease which would ascribe fundamental significance to these observations is probably not warranted upon the basis of any evidence yet accumulated. In his exhaustive

review, Leiter (1931) expressed doubt that the incidence of such rates is any greater than might be expected to occur secondary to undernutrition, therapeutic diets, inactivity and possibly other factors not directly related to the intimate nature of the malady

In nephrotic cases a number of observers—Campanacci, Eppinger, Epstein, Liu Molnár and others—have reported the favorable production of diuresis by the employment of enormous doses of thyroid substance. The results are by no means always obtained, but the fact seems to be established that individuals exhibiting the low basal metabolic phase of the malady can sometimes tolerate astonishing amounts of this ordinarily very toxic agent. Epstein gave as much as 4 Gm (60 grains) of desiccated thyroid daily. One patient received 1.5 Gm (22 grains) daily for five months followed by a total of 137 mg of thyroxin in eleven weeks with no striking effect on the basal rate and no symptoms of toxicity. Platt failed to demonstrate thyroxin in the urine of one of the nephrotic patients while being dosed in the above extravagant manner. Leiter believes that this is not true hypothyroidism in spite of the rate, that a tolerance above normal may be found in other edematous states and that the matters of absorption, destruction, and excretion need to be studied in view of the differences between this sort of reduced metabolism and that encountered in true myxedema. Both Mitchell *et al* (1938) and Farr (1938) failed to find metabolic rates above normal in nephrotic children. Lueth (1941) has used thyroid substance almost routinely in $\frac{1}{2}$ grain (0.03 Gm) doses 3 or 4 times daily but has not seen beneficial results. Page (1940) has found the drug useful only when combined with anterior pituitary extract.

Cathartics—Some physicians favor the daily use of a saline cathartic, but the practice certainly makes it impossible to maintain any exact knowledge of the patient's ability to eliminate through the kidneys. Proprietary saline mixtures should not be used unless it is positively known that they contain no other salts than the nonabsorbable ones desired to produce the cathartic effect. The following salines are effective.

Magnesium sulfate (Epsom salt) $\frac{1}{2}$ to 1 ounce (16–32 Gm). It is worthy of note that Hirschfelder and Haury (1934) described a clinical syndrome of high plasma magnesium accompanied by somnolence and coma, which may be induced by the oral administration of Epsom salt in patients with renal insufficiency.

Magnesium citrate principally used as the solution of magnesium citrate, an effervescent preparation in 12-ounce bottles, dose, 1 bottle or less. Milk of magnesia can be converted in part into magnesium citrate by the addition of a fruit acid such as lemon or orange juice.

Sodium sulfate (Glauber's salt) dose $\frac{1}{2}$ ounce (16 Gm).

Potassium and sodium tartrate (Rochelle salt) dose, 2½ drachms (10 Gm).

Sodium phosphate dose 1 drachm (4 Gm), there is also a pleasant effervescent preparation with a dose of 2½ drachms (10 Gm).

Compound effervescent powder (Seidlitz powder) dose, the contents of one blue paper (sodium bicarbonate and Rochelle salt) and of one white paper (tartaric acid), dissolved separately in water, and then mixed.

Compound jalap powder (1 part jalap, 2 parts potassium bitartrate flavored with ginger) 10 to 60 grains (0.6–4 Gm) daily, stirred into $\frac{1}{2}$ cup of warm water.

Mechanical Measures—Extensive hydrothorax or abdominal ascites, if causing respiratory embarrassment, is usually relieved by paracentesis. Bland and White (1930) read a paper on the use of the Southey tubes, which provoked considerable discussion and revealed that the profession at that time at least still had considerable faith in the efficacy of mechanical drainage of fluid from the edematous legs following the opening of the skin. Several years later, Leach (1936) described an improved type of Southey tube. Goldring (1941) has recently expressed the belief, which is probably shared by most members of the profession, that the danger of infection with the Southey tubes is too great to warrant their employment in most instances, though I think the fact should not be overlooked that in selected cases as suggested by Beck (1939), the judicious use of sulfonamides might considerably lessen this risk. Acupuncture (six or more punctures in either extremity with an 18 gauge needle) and the making of long deep incisions, are the older methods and have their very great efficacy marred considerably by the many obvious disadvantages associated with causing the person and bed of the patient to be soaked in fluid, for the patient able to sit up with the feet in a small tub they are excellent.

In Pemberton's (1932) opinion, the value of gentle massage in promoting redistribution of fluid is too much overlooked in this country. Page (1949) has expressed the same opinion and shares with many the feeling that bed rest and no exercise are not to be advised for the edematous patient unless there are absolute indications for such immobility.

ANEMIA

The anemia of chronic nephritis is well known, much studied and still not understood. The latest reported investigation I have seen, that of Norden son (1938), in Sweden, indicates that there is a depression of erythropoiesis but a clear explanation of the cause of this depression is not revealed in the work. Townsend *et al* (1937) consider lowered gastric acidity a contributing factor. This anemia responds very poorly to iron salts, liver and stomach preparations. Transfusions are of course frequently given but their effect is only temporary.

HYPERTENSION

The hypertension of arteriosclerotic nephritis is a part of the cardiovascular renal syndrome and from the therapeutic standpoint it is idle to attempt a separate consideration (see Essential Hypertension).

THERAPY OF TERMINAL NEPHRITIS

The beginning of the end is recognizable by appearance or intensification of the eyeground changes, intensification or perhaps initial appearance of hypertension, and laboratory evidences of reduction in renal function. With the approach of uremia edema may disappear because of the destruction of so many glomeruli that a high rate of protein loss cannot be maintained, often however, it is replaced by the edema of congestive heart failure. In a very interesting recent report, Gouley (1940) describes a peculiar type of myocardial degeneration which he considers characteristic of the failing heart in uremia, the pathogenesis of uremic heart failure has not been satisfactorily explained.

The chief aim of treatment at this time is to make it possible for the patient to enjoy life as much as he can until the end. Restrictions should be relaxed and the relatives told of the state of affairs so that they can help as much as possible. Page (1940) well says "It is, I think, a therapeutic achievement when the patient walks into the hospital and dies a few days or weeks after admission."

Diet—Nothing is to be gained by any special dietary restrictions at this stage so it is well to allow the patient to choose just about what he likes. Theoretically a moderately low protein intake would be desirable in order to keep down nitrogen retention, but as a matter of fact if insufficient protein is supplied for satisfactory tissue nutrition the balance is obtained from endogenous sources and the end result is the same as regards nitrogenous products to be eliminated. The chief problem usually is to get the patient to eat enough of anything for the appetite has usually much decreased at this stage, sometimes even the use of a small amount of wine or a cordial is justified in the attempt to stimulate it.

Sodium Chloride—Often toward the end the kidneys have lost the ability to concentrate urine so markedly that large amounts of chlorides may be washed out. It is therefore well to study the plasma chlorides if possible and to administer sodium chloride (the reverse of what had been done up to this time) in an amount of 3 or 4 Gm daily together with sufficient water so that they will be washed out and not retained to induce edema afresh. The way has to be felt carefully in each case and if there is a complicating heart failure the administration of chlorides will simply have to be abandoned.

Hypertension—There is nothing one can do about this after it has become permanent.

Pallor—Patients are often distressed by their ghostly appearance. Page (1940) counsels sunlight or plentiful use of the ultraviolet lamp to bolster morale.

Heart Failure—Digitals and fluid and salt restriction are indicated as in any other failure (see Congestive Heart Failure). The uremic patient usually tolerates digitals or ouabain very well. It is usually considered to be undesirable under the circumstances to employ diuretic drugs.

Acidosis—In the terminal stages of nephritis, acidosis is usually present to a marked degree. Indeed, I am sure that many observers will agree with Marzullo's (1940) statement that the severity of the symptoms of advanced nephritis and uremia is directly proportional to the degree of acidosis and not always or exactly to the extent of nitrogen retention. Phosphates and sulfates are retained in the blood, there is decreased formation of ammonia by the kidneys, and as a result direct depletion of the alkali reserve takes place. This depletion is sometimes even augmented by an increased excretion of alkali by the kidneys and the loss of additional base through vomiting, for in advanced nephritis the free hydrochloric acid in the stomach is often very small in amount.

Undernutrition is also well known to promote acidosis. Mitchell and Guest remind us of the faulty synthesis of glycogen in acidotic states as an important factor in the poor development and growth of young nephritics. Even in the severe acidosis of advanced cases, the necessity for a too great reduction of protein will not arise if we heed the report of Lyon *et al* (1931), whose careful work showed that the readjustment of the diet to give an alkaline ash will

often result in a decrease in the acidity and considerable amelioration in symptoms, measures by which this may be accomplished are reduction in meat, rice, macaroni, bread, cereals, increase in fruit and vegetables, addition to the diet of figs, molasses and raisins. If the patient remained on an acid diet, Lyon was able to overcome its acidifying effect, while retaining all the advantages of feeding meat, etc., by supplementing it with sufficient alkali by mouth to keep the urine alkaline, in some instances he had to do this even though a basic diet was being employed. In the presence of coma, Plotz *et al* (1937) give 150 to 200 cc of 4 per cent sodium bicarbonate solution intravenously at six- to twelve hour intervals for three or four doses.

Itching—This is often a most distressing symptom and one difficult to relieve. Sponging, not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. Other measures are discussed under Portal Cirrhosis.

Nausea and Vomiting—I have never seen or heard of measures really effective in checking this vomiting, though of course the whole gamut of usual procedures is run through: ice sucking, sedatives, fresh air, etc. Correction of acidosis is the best preventive.

Convulsions—In accordance with the belief (which is probably wrong) that it is the high nonprotein nitrogen content of the blood *per se* which induces the fatal termination in uremia, sweating would be theoretically indicated because the perspiration contains 30 per cent more of these retention products than does the blood. However, even though induced only by the use of hot-water bags and plenty of blankets, sweating is a very debilitating activity. A hypodermic of $\frac{1}{4}$ grain (0.005 Gm) of pilocarpine nitrate is very effective in bringing out the perspiration, but it also not infrequently causes vomiting and hiccup, and may bring about collapse with a very slow pulse. If there are pulmonary complications the danger of precipitating pulmonary edema with this drug is very great. If there are twitches and tetanoid convulsive movements the possibility of hypocalcemia should be borne in mind. Calcium may be employed as in tetany, but not parathyroid extract unless the necessity seems very urgent, for there is some evidence (Highman and Hamilton, 1937) that the activity of the parathyroid glands is increased in chronic nephritis. Shelling and Hopper (1936) also advise against the use of viosterol and cod liver oil, they may raise the phosphate as well as the calcium level of the blood. Ordinary restlessness and even delirium may be combated with the sedatives and hypnotics (discussed under Insomnia), but morphine or dilaudid may have to be resorted to. It is worthy of note that the correction of acidosis is a powerful weapon against the occurrence of convulsions, but when in spite of these measures true uremic convulsions and coma supervene there seems to be nothing to do that is worth the doing.

DISTURBANCES CAUSED BY EXCESSIVE HEAT

DISTURBANCES CAUSED BY EXCESSIVE HEAT

HEAT EXHAUSTION

This the most common form of disturbance caused by an excessively warm environment, is known in the South as "a touch of the sun" or "over come by the heat." The individual suddenly becomes acutely sensitive to the oppressive atmospheric conditions, grows pale with a clammy skin, has disturbances of vision, feels very weak and perhaps nauseated and either crumples down in the sun or manages to drag himself into the shade before collapsing, the pulse is fast and weak, the respirations rapid and shallow, the pupils dilated, temperature normal or subnormal. The mortality from this type of heat stroke is practically nil, but the patient often recovers very slowly and is thereafter likely to be unusually sensitive to high temperatures.

THERAPY

The patient must be made to lie in the coolest place available, his clothing should be opened and he should be given water to drink if he desires it. If the pulse remains rapid and weak for long, one of the stimulants (see Index) may be advantageously used. Occasionally in these cases the temperature falls quite far below normal and it becomes necessary to apply external heat and administer hot drinks, one should be careful here as a sudden high rise of temperature may be induced.

HEAT STROKE

(Heat Retention)

The severe and frequently fatal form of disturbance caused by excessive heat is characterized by a brief prodromal period not easily distinguishable from that occurring in ordinary heat exhaustion (see above), but consciousness is early lost and it is noticed that the skin, instead of being clammy, is dry and hot and that the temperature is very high. The pupils are usually dilated in the beginning, but the pulse is rapid and full and the breathing deep. It is only later that the pulse becomes irregular and feeble and the respirations become shallow and finally of the Cheyne-Stokes type, at this stage the pupils are found to be contracted and the conjunctivae injected. In many cases involuntary passage of characteristically foul feces takes place and the patient's body odor also becomes offensive. Muscular twitches and rolling of the head are common, sometimes epileptiform convulsions take place. As death approaches evidences of pulmonary edema are sometimes to be found. Old age, degenerative disease, and acute alcoholism seem to predispose very markedly to heat stroke.

THERAPY

Attempt must be made to stimulate the heart and the respiratory center by the use of stimulants, and it is sometimes necessary to administer chloral and bromide by rectum to control the convulsions, but the most imperative need is to reduce the temperature. The following methods are employed:

(a) Place the patient in water cooled to 50° F. (10° C.) by floating a cake of ice in it, and keep him there until the rectal temperature falls to 102° F. (38.8° C.). After this temperature is reached the body will continue to lose heat in favorable cases even after removal from the water; sometimes the fall will go below the normal line. It is imperative that vigorous manual friction of the skin be made continuously while the patient is in the tub, for unless hyperemia takes place the overheated blood will only be driven in instead of being cooled at the surface. In a study of 44 cases of heat stroke during a short severe heat wave in Cincinnati in 1938, Ferris *et al.* found ice water tubbing with massage the most satisfactory first method of approach.

(b) Injection of 1000 cc. or more of ice water into the rectum. This method is very little employed in the large clinics where many of these cases are seen each summer.

(c) Rubbing the body with ice, or placing the patient in sheets wrung out of ice water. These methods also are looked upon as less efficient than the following:

(d) The abstraction of heat by evaporation of water from the body surface. This is best accomplished by spraying water onto the stripped body from a fine nozzle, meanwhile maintaining a constant current of air either by means of hand or electric fans. There is no advantage in using ice water as tepid water will remove practically as much heat. This method has replaced all others in most hospitals, and has the added advantage that it can be utilized anywhere since it does not depend upon the use of ice; Elkins, reviewing the subject in 1938, goes so far as to say that ice water baths, ice water enemas and packs should never be used. When the rectal temperature reaches 102° F. (38.8° C.) the evaporation may be stopped during a period of observation. Hearne, with the British troops in Mesopotamia, found that the cessation of sweating, once it has been established, is a valuable sign of impending recurrence, and that if these patients are covered with a moist sheet and the fanning resumed, artificial perspiration will be established and recurrence sometimes averted.



HEAT CRAMPS

(Stokers' Cramps)

This is a type of heat exhaustion seen frequently in those who labor in the heat of firerooms, in deep mines, etc. Following a period of muscular twitching, the patient is seized with violent cramps principally of the abdominal groups; sometimes, however, the spasm is so general as to resemble an epileptic attack. The patient is nauseated, dizzy, stuporous, and usually

pallid and perspiring, the pulse is rapid but strong and the temperature little if at all above normal. Urine is scanty and there is usually great thirst. These attacks are believed to be due to the fact that in the excessive ingestion of water and its elimination through the skin abnormal quantities of chlorides are lost, though just why this loss of chlorides should cause the cramps is not clear.

THERAPY

The sufferer must be removed to the coolest place available and be allowed complete rest. The opiates are almost completely ineffective in lessening the cramp or pain, but rest alone suffices in most instances. Talbott (1935), reviewing the literature, his experience with Michelsen during the construction of Hoover Dam, and his own observations in the Youngstown mills, states that the only reliable as well as rational remedy in severe cases is the intravenous administration of physiologic saline solution, 600 to 1000 cc., and repeated if the patient is much dehydrated. Thereafter 15 grain (1 Gm.) salt tablets are given by mouth every hour until fifteen have been taken, or the patient is put on an exclusive diet of milk, in large quantities, for twenty four hours.

Prevention consists merely in the ingestion of sufficient salt, though the mistaken idea that dextrose is protective is apparently widespread. Salt may be taken in the form of a 15 grain (1 Gm.) tablet each time water is drunk. Most workmen object to swallowing the tablets; however, Talbott states that the best way of supplying salt is to place it in the drinking water in a concentration of 0.1 per cent, he says that such a solution does not have a perceptible saline taste and allays rather than promotes the sensation of thirst.

The workmen themselves realize that the better their general condition the less likely they are to develop cramps.

THE ANEMIAS

THE ANEMIAS

So much progress has been made in hematology in recent years that the hallowed separation of all anemias into "primary" and "secondary" types has had to be superseded by more rational classifications. Undoubtedly the most useful of these for scientific purposes approaches the subject from the standpoint of the size and color of the erythrocyte as indicative of the pathogenesis of each of the maladies, but I doubt if such a classification has as yet been perfected to the point of being of greatest therapeutic service. Therefore in this chapter I am considering the several anemias according to an arrangement designed to facilitate and expedite their satisfactory treatment.

ANEMIAS PRIMARILY BENEFITED BY IRON THERAPY

Nutritional Anemia of Infants—The normal infant, born into the world with many more erythrocytes and much more hemoglobin than is needed for extra uterine life, rapidly and proportionately loses both (icterus neonatorum often evidencing the destruction that is going on) for about six weeks, and more slowly to about the tenth week, after which the values slowly rise again to the fifth or sixth month. This period of "physiologic" anemia usually requires no treatment, but the abnormal condition of the blood frequently seen in infants between six months and two and one half years does call for the institution of therapy. It is a true anemia in which, though the erythrocyte count may be high, low or normal, the cells are smaller than normal (microcytosis) and are subnormal in hemoglobin content (hypochromia), and there is a low hemoglobin content of the whole blood. Enlargement of liver, spleen and lymph nodes, and slight edema of the extremities, are sometimes seen, but the youngster usually appears to be in a good state of general nutrition, pallor is of frequent occurrence but alone does not necessarily indicate the presence of this type of anemia. Gastric acidity is sometimes decreased. The low iron content of human and cow's milk is responsible for the malady, which will appear (a) if the amount of iron stored in the fetal liver during intra uterine life has not been sufficient to carry the infant until mixed-diet feeding can begin, or (b) if the mother has received insufficient iron in her dietary during pregnancy, or (c) if the infant is one of twins or is born prematurely.

Chlorosis—This disease, usually thought to have quite generally disappeared, has the following characteristics: (a) occurrence practically exclusively in girls of the servant class between puberty and twenty five years of age, (b) anemia characterized by moderate or perhaps no reduction in the number of erythrocytes but with a variable reduction in their size and a hemoglobin content so low that in a stained preparation the cells appear definitely achromic, often being mere rings, there is frequently a striking

thrombocytosis (c) greenish pallor, most marked about the eyes and chin, (d) the usual signs of severe anemia, such as breathlessness, irritability, and edema of the extremities, and often, in these cases, puffiness of the face, (e) constipation and dyspeptic disturbances, perverted appetite, low grade fever, and often irregular or scanty menses. Recent reviews indicate that hyperacidity was not so regularly present as has been believed. Nowadays it is recognized that a large number of these girls certainly had peptic ulcer or tuberculosis. Very interestingly, Patek and Heath (1936) state that chlorosis has not disappeared, reporting 4 cases that had entered their clinic in the preceding two years. Olef (1937) is also able to report 3 cases recently seen. Patek and Heath define the malady as merely the exaggeration of a normal tendency toward anemia in adolescent girls created by the increased demand for iron made by growth and by menstrual or other blood loss and by diet deficient in iron-containing foods, and they remind us that Stockman very soundly pointed out these things as long ago as 1895.

Idiopathic Hypochromic Anemia—This entity has been recently described under a variety of names: achylic chloranemia, simple achlorhydric anemia, idiopathic hypochromemia, hypochromic anemia with achlorhydria, primary hypochromic anemia, chronic chlorosis, etc. Most of the patients are women between the ages of thirty and fifty years, though the disease is not unknown in men. There is a host of symptoms, which probably prevented the earlier recognition of the syndrome as a unit, however, the principal ones are partial or complete achlorhydria and achylia, anorexia, tongue appearance like that in pernicious anemia, paresthesias and other nervous changes (if there is difficulty in swallowing—probably due to esophageal spasm—one speaks of the Plummer-Vinson syndrome), fingernails and toenails with spoonlike depressions, enlargement of the spleen in one third to one half of the cases, discomfort and flatulence following meat so that carbohydrates are mostly eaten, possibly diarrhea, menstrual disturbances, systolic murmurs over the whole precordium and perhaps some degree of cardiac dilatation, pallor, chronic fatigue, a blood picture practically indistinguishable from that of chlorosis, and a history which reveals the symptoms to be of long standing.

Fowler and Barer (1937) concluded that this is usually a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of iron due to deficient gastric secretion. Meyers *et al* (1938) found one or other of the following factors in the probable etiologic role in many of their cases: deficient meat and iron intake, deficient gastric acidity and other digestive disturbances, hypothyroidism, multiple pregnancy, menorrhagia and other forms of bleeding. They classified 24 per cent of their patients as constitutional psychopathic inferiors. Lundholm (1939), in an extensive study of the subject in Sweden, recognized hemorrhage as important in the development of this anemia but was unable to correlate the amount of blood lost at menstruation with the degree of anemia, very interestingly, however, he feels that there is an hereditary factor concerned in the etiology.

Anemia of Gastro-intestinal Surgery—The majority of the cases of anemia following gastrectomy and gastro-enterostomy are of the simple hypochromic type just described above.

Anemia of Chronic Blood Loss—The rate at which the erythrocyte and hemoglobin content returns to normal in a healthy person after a single severe hemorrhage varies widely with individuals but in, perhaps most

instances cell return is completed in four to six weeks and pigment return in six to eight weeks. Neither iron nor liver administration is indicated in these cases ordinarily, the presence of chronic infection will considerably retard recovery. Patients chronically bleeding oftentimes present the picture of a severe hypochromic microcytic anemia—the type in which iron, but not liver, is strongly indicated.

Anemia of Pregnancy—Pregnancy may of course supervene upon any of the anemic states, and in itself may be responsible for anemia following hemorrhage or incident to toxemia or sepsis but excluding these things, there are anemias of quite other causation. One of these is seen with such regularity that it has come to be called the ‘physiologic anemia’ of pregnancy—a steady decrease in both erythrocytes and hemoglobin to about the end of the second trimester. Increasing knowledge of blood volume changes has now shown this to be only a reflection of hydremia—dilution of the blood causes it to appear poor in cells and hemoglobin. The true (and they are often severe) anemias were shown by Strauss and Castle, in 1932, and by others since, to be almost always of the hypochromic type described above and to occur as the result of a direct dietary deficiency or a deficiency consequent upon impaired gastric secretion. Rarely the anemia is of the macrocytic type benefited by liver therapy, which is to be discussed later.

Hookworm Anemia—In the anemia consequent upon *ankylostoma* infestation, which is really an anemia due to chronic blood loss, the erythrocytes are markedly reduced in number and in size, hemoglobin is diminished to an even greater extent proportionately. This is, then, a hypochromic microcytic anemia such as the others already discussed.

THE ADMINISTRATION OF IRON

It seems that the upper part of the small intestine is the chief site of iron absorption and that the soluble ferrous salts are the most easily absorbed and assimilated, indeed it is probable that all other forms of iron must be reduced to the ferrous state before their utilization becomes possible. The nuclei of erythroblasts in the bone marrow take up the iron conveyed thither in the blood plasma, when hemoglobin has been formed from it the nuclei are extruded and the ‘mature,’ non nucleated, hemoglobin bearing erythrocytes pass into the circulation. Under the influence of iron there is an increased rate of delivery of erythrocytes from the marrow for a time and even reticulocytes—the last stage before full maturity—enter the blood stream in the early stages of iron therapy the reticulocyte count affords an index of the patient’s response to treatment. It is usually felt that average hemoglobin regeneration occurs at the rate of 1 in 2 per cent per day, the height of the effect being reached between the twenty fifth and fortieth days. But dosage must be correct for there is a definite ‘threshold’ which must be passed before response is obtained. All the signs and symptoms of anemia may be caused to disappear but the ability to secrete hydrochloric acid will rarely be restored if it has been completely absent. When iron is subsequently omitted the patient is extremely likely to relapse no matter how large an amount of the metal has been stored. It would seem that this sequestered iron constitutes, in the words of Witts (1936), ‘a frozen credit which they cannot liquefy’.

Choice of Preparations—General intoxication from the administration of iron by mouth practically does not occur (only 1 case has been recorded Hurst, 1931), the drug may be given by mouth even to patients with a bleeding peptic ulcer or with ulcerative colitis. Effective doses cannot be given parenterally, however, without incurring the great risk of a severe reaction (too little work has as yet been done with the iron ascorbate of Friend [1938] to constitute a contradiction of this statement). We shall therefore consider only preparations for peroral administration, and of these only those which are most favored by leading students of anemia (Table 20). It is best in using any of them to begin with small doses and take several days to work up to full doses, thus lessening the likelihood of gastro intestinal upset.

TABLE 20—IRON SALTS FOR ADMINISTRATION BY MOUTH

Salt.	Daily dosage		
	Adult.	Children	Infants to 4 yrs.
Ferrous sulfate	12 grains (0.8 Gm.)	10-12 grains (0.6-0.8 Gm.)	6-8 grains (0.4-0.5 Gm.)
Reduced iron	45 " (3.0 ")		
Ferrous carbonate (Bland's pill)	90 " (6.0 ")		
Ferric ammonium citrate	90 " (6.0 ")	60-90 grains (4.0 Gm.)	15-45 grains (1-3 Gm.)
Ferric pyrophosphate			21 grains (0.15 Gm.)

Ferrous Sulfate—The least likely of all the salts to cause gastro intestinal irritation, especially if given just after meals, it is perhaps best to have one dose taken after each meal and one on retiring. Ferrous sulfate oxidizes to the less effective ferric compound when exposed to air, but the 3 grain (0.2 Gm.) coated commercial tablet is stable. Mackay and Jacob (1937) found that the salt keeps more than two months at room temperature if mixed in solution with dextrose and a small amount of hypophosphorous acid, the following prescription may be written for an infant.

- Rj Ferrous sulfate 5iss 60
 Dilute hypophosphorous acid (U.S.P. IX) ʒiiv 10
 Dextrose ʒiij 60.0
 Chloroform water to make ʒviij 250.0
- Dissolve the dextrose and ferrous sulfate in separate portions of chloroform water, then add the acid to the dextrose portion. Mix the two portions and make up to volume with chloroform water.
- Label: 1 teaspoonful four times daily in water, milk or fruit juice. (The teaspoonful will contain 1½ grains [0.1 Gm.])

It is best not to use iron in solution in treating adults as it may stain the teeth even though taken through a tube, however, the discoloration is superficial and may be removed by thorough "cleaning" of the teeth by a dentist.

Reduced Iron—This drug is insoluble and must therefore be given in

capsule form, it can be suspended, of course, but the offering of such a for bidding dose to the patient is inexcusable, of course for infants one can prescribe any of the iron salts in capsules and then empty the contents of a capsule into orange juice which is well stirred while being drunk. Any older child or adult can easily swallow a capsule containing $7\frac{1}{2}$ grains (0.5 Gm) of reduced iron. The average adult dose would require the taking of 6 such capsules during the day. Warrant for the contention that this preparation is best taken before meals would be difficult to produce, I think, for so many of these patients are achlorhydric.

Pill of Ferrous Carbonate (Blaud's Pill)—The coated pills nowadays obtainable keep well enough, but they tend to become very hard and doubtless sometimes pass through the intestinal tract undissolved. Some men have them powdered by the druggist and packed into capsules (it is well to provide one capsule per pill). Ferrous carbonate does not tend greatly to disturb the gastro intestinal tract, but the patient must take 60 pills daily in order to receive full adult dosage.

Ferric Ammonium Citrate—This salt must be given in high dosage and gastro intestinal irritation from it is not unusual. It is very soluble and may well be prescribed as follows for the adult who would require the average full dose.

R. Ferric ammonium citrate (powdered)	3ij	60.0
Syrup of cinnamon (N.F.) to make	3v ij	250.0
Label: 2 teaspoonfuls in water, milk, or fruit juice three times daily (The teaspoonful will contain 15 grains [1 Gm] of the iron salt.)		

This preparation is perhaps more likely to stain the teeth, even though taken through a tube, than is the solution of ferrous sulfate. Ferric ammonium citrate may also be prescribed in capsules, one of convenient size will hold 4 grains (0.25 Gm).

Ferric Pyrophosphate—Elvehjem (1937) used this preparation satisfactorily in infants, it seems to have the advantages of being quite soluble, practically tasteless, and not astringent. A prescription employing it will be found below.

Potentiation of Iron with Copper and Other Substances—Convincing evidence has not been offered that the addition of copper to iron therapy is of any value in the iron-deficiency anemias of adults. Indeed Fowler and Barer (1941) seem positively to have shown that it is not. But the investigations of such workers as Elvehjem *et al* (1933-1937), Usher *et al* (1935), Josephs (1931), and Hutchison (1938), indicate that in some instances of nutritional anemia in infants the addition of small amounts of copper to the iron will cause the maximum regeneration of hemoglobin. Many American pediatricians hold the view expressed by Smith (1936), that although the same results may probably be accomplished by substituting another iron salt, or increasing the dose of the original preparation, the introduction of a small copper supplement should be kept in mind when simple nutritional anemia becomes refractory. Some Continental and British students do not feel, however, that copper is of value under any circumstances. A few men think that copper ingestion may incline individuals toward the development of hemochromatosis, but they are probably wrong. An amount of copper sulfate which will give $\frac{1}{10}$ grain (0.003 Gm) to the dose—3 grains (0.18

Gm) added to any of the preceding 8-ounce (250 cc) prescriptions—may be used, or the following prescription which I have modeled upon the solution used by Lliebjem may be written

R Ferr c pyrophosphate	5iss	10 0
Copper sulfate	gr iij	0 18
Alcohol	5i j	12 0
Cinnamon water to make	3viij	250 0

Label 1 teaspoonful daily in milk or fruit juice

There have been some indications that other elements, particularly manganese, germanium, cobalt and calcium, and also the substance chlorophyll, have some influence upon iron utilization, but as yet no practical applications that are convincing have been offered. The study of Patek and Minot (1934) suggested that in certain cases of iron-deficiency anemia in adults there may be also a deficiency in some useful material contained in hile pigment, but I have heard nothing further of this.

Since iron seems to be either better absorbed from an acid than from an alkaline medium, or is absorbed in a more readily available form, and since many patients with one or other type of iron-deficiency anemia are also deficient in gastric acid, the assumption is quite naturally made that hydrochloric acid should be administered as in the treatment of hypochlorhydria *per se*. The fact of the matter is, however, that no clinical study has ever convincingly shown that such therapy has value from the standpoint of increasing the effective utilization of iron, the latest study of this nature that I have seen (Pohle and Heath, 1939) indicated that neither acid nor alkaline salts in large amounts affected the utilization of iron. In some instances acid may undoubtedly help allay the dyspeptic symptoms which frequently afflict these patients, but it may also aggravate these symptoms.

Patients with the iron-deficiency anemias do not ordinarily profit by the addition to the iron regimen of the liver and stomach preparations used in pernicious anemia, or of the so-called 'secondary anemia liver extract,' or of yeast or wheat germ preparations. Castle and Minot (1936) write 'We have never observed a case of hypochromic anemia which would not respond to iron, but which would respond to whole liver or to some fraction of liver.' They add that in rare instances iron alone will not bring the hemoglobin quite up to normal and that the addition of liver in these cases will do so, but that also the use of a proper diet will serve as well. However, it should be remarked that Hartfall's (1934) study of postgastrectomy and gastro-enterostomy anemias indicated that it may sometimes be profitable to consider these cases as partaking of the features of both hypochromic-microcytic (iron-deficiency) and hyperchromic macrocytic (liver stomach deficiency) anemias, and treat accordingly.

Dietetics—Nowadays, infants are got onto solid foods much more rapidly than used to be the case. cereals (pabulum is said to be high in iron) at the third month, eggs, fruits, and puréed vegetables between the fifth and seventh months, meat at ten months. In addition to supplying muscle and bone building substances and vitamins such a well rounded dietary also keeps pace with the need for iron. But as a matter of fact we do not know just which foods are the best from the latter standpoint. Of course elaborate tables of the iron content of foods are available, but studies in

recent years have shown that the iron content of a food and the availability of that iron for hemoglobin production are often quite different things. It will require much laborious work still before we shall be able to say precisely that this or that article of food is to be preferred for its contribution of iron. Such dietary procedure for infants as that indicated above and for adults insistence upon the liberal use of red meat, eggs, green vegetables, and fruits, remain our best guides, but dietary measures alone are of practically no value in combating this group of anemias—the carefully studied patients of *Mettier et al* (1939) failed to be benefited in the least by an "iron rich" diet taken for a long time, but the bone marrow responded rapidly and excellently when large doses of iron were added.

Routine Administration of Iron in Pregnancy.—A number of modern studies has been increasingly indicating the advisability of the routine employment of iron after the middle of pregnancy, that of *Bethell et al* (1939) is a recent example. Not all obstetricians agree on the point, however, for some, like *Labate* (1939), believe that since only 50 per cent of women develop anemia during pregnancy it is sounder practice to check the blood status several times during the period and give iron only when indicated. Nevertheless, the evidence of *Corrigan and Strauss* (1936) in favor of routine use of iron seems rather convincing. One hundred members of a group of 200 normal pregnant women were given iron, the alternate 100 being used as controls, observations began when the women were from three to seven months pregnant, the average one hundred and sixty two days. There were no important dietary or blood level differences between the two groups. Determinations one week postpartum revealed that in the treated group (a) the hemoglobin average was 85 per cent (a gain of 12 per cent over their average in the beginning), (b) none of the women had a hemoglobin below 70 per cent, (c) the erythrocyte count had risen from 3.72 to 4.28 million per cubic millimeter. In the untreated control group (a) the hemoglobin average was 75 per cent (just what it had been at the beginning), (b) 24 per cent had a hemoglobin below 70 per cent, (c) the erythrocyte count had risen from 3.88 to only 3.94 million per cubic millimeter.

Routine Administration of Iron in Infancy.—*Mackay*, in England is well known as a champion of the opinion that routine iron therapy in the latter months of pregnancy is not enough, and that, at least in the inhabitants of an impoverished area, routine dosing of infants with iron is also urgently needed. Here and there voices are in agreement with her, but nothing to speak of is done in the matter, I believe.

Transfusion.—In these days of furious speed—"super" trains and air planes, pictures from the battle fronts before the ship has gone down or before the land engagement has fairly begun, and so on—there is burgeoning a school of impatient therapists who can wait for nothing. To a man, these chaps fume for blood transfusion in the anemia of pregnancy—if the husband can afford it.

ANEMIAS PRIMARILY BENEFITED BY LIVER-STOMACH THERAPY

Pernicious Anemia.—Pernicious anemia is a chronic deficiency disease which progresses, usually with remissions, to a fatal issue unless we supply the patient adequately with a certain specific substance which his own economy has failed to produce, in which case the chief manifestations of the disease can be held in abeyance apparently for an indefinite period of time. The outstanding feature of the disease is the peculiar macrocytic-hyperchromic anemia, accompanied by thrombocytopenia and the appearance of numerous many lobed polymorphonuclear cells, though there is usually an absolute leukopenia and neutropenia. The number of red cells is usually below 2,000,000, counts of 500,000 or less not being unusual. Hemoglobin is somewhat reduced but not in proportion to the reduction in the number of red cells, consequently there is always a color index higher than one. In addition, there is marked anisocytosis with macrocytes predominating, marked poikilocytosis, and diffuse and punctate polychromatophilia. A variety of nucleated red cells, and occasionally mitosis, are seen (Warning: gastro-intestinal carcinoma can give a blood picture astonishingly like this!). In the beginning of a remission there is an increased number of reticulated red cells. The findings of Dameshek and Valentine (1937) show that the changes in the marrow are accurately portrayed by this picture of arrested maturation and malformation presented in the peripheral circulation. The van den Bergh (indirect) reaction is increased. Very interestingly, Warner and Owen (1942) find that patients in relapse frequently show considerable decrease in plasma prothrombin, this hypoprothrombinemia not responding to the administration of vitamin K, but disappearing when specific liver therapy is instituted.

Symptomatically the onset is insidious, the patient usually appearing for the first examination with most of the characteristic symptoms present in some degree. There is complaint of languor, muscular weakness, and shortness of breath on exertion. As a rule there is little or no weight loss in the beginning, but if the gastro-intestinal symptoms are marked the patient not infrequently becomes thin. In these days of earlier diagnosis the characteristic lemon yellow tint to the skin is seen less often than a simple pallor. A heart murmur of the 'bemic' type is almost the rule, and symptoms of angina pectoris are sometimes quite prominent. Slight puffiness of the ankles is a frequent finding, in rare cases the edema is much greater. Fever, or the opposite, a subnormal temperature, may characterize a severe relapse. And then there are, in addition, the gastro-intestinal and central nervous system symptoms. The former may at one time or another include all the dyspepsias, with periods of diarrhea or apparent gallbladder disturbance being especially prone to occur, tongue and stomach findings are the most constant. The tongue is off and on sore and raw, particularly around the edges, and may at times be slightly ulcerated, it is nearly always smooth, red and glazed and without any furring. The chief finding of moment in the stomach is a great diminution in HCl, in fully established cases, with extremely rare exceptions there is a constant achylia. Careful examination will reveal involvement of the central nervous system in at least 80 per cent of cases. Paresthesias are most frequent, but diminution in the objective senses, such as to vibration and posture, and other evidences of posterolateral sclerosis are not unusual, indeed

it is the consensus that in the absence of ergotism, syphilis, pellagra, arterio sclerosis and cachectic states (in all of which, as a matter of fact, the anatomic changes are distinctly different from those in the sclerosis of pernicious anemia), all cases of subacute combined degeneration of the cord are in reality cases of pernicious anemia. However, Palmer and Porter (1936) reported 1 case and Suh and Merritt (1938) 8 cases of such degeneration without the typical blood findings of pernicious anemia. Palmer and Porter's patient experienced a prolonged spontaneous remission of symptoms, and 4 of the 6 patients treated in Suh and Merritt's series responded well. Except for the changes in the cord, central nervous system involvement is rare though pernicious anemia patients are generally irritable and extremely difficult to handle, definite psychoses are occasionally encountered, but Osgood (1935) believes that they are probably largely incidental. In some instances the occurrence of neurologic signs precedes other manifestations by a considerable period, Sanford (1935) has reported 3 cases in which prompt liver therapy entirely prevented the appearance of hematologic evidences of the disease, perhaps Palmer and Porter's, and Suh and Merritt's cases, mentioned above, could be simply explained on this basis. Bigg (1940) has shown that splenomegaly is rare, for in a series of 200 consecutive cases the spleen could be palpated in only 3 per cent. Marked enlargement of the liver is not frequently noted in the living patient, but at autopsy both the organs are found to be somewhat enlarged. Other constant findings at autopsy are the extension of hyperplastic red bone marrow into portions of the medullary cavity of the long bones ordinarily occupied by fat only, the 'tiger lily' appearance of the heart, the presence of hemosiderin granules in a number of the organs, and, in many cases, the presence of foci of sclerosis in the cord and sometimes in the brain also. Marked atrophy of the gastric mucosa is said to be characteristic, but Jones, Benedict and Hampton (1935) have been led to believe by their studies in the living—direct, gastroscopic, roentgenologic, and biopsy observations—that atrophy is not an invariable accompaniment of the disease but occurs particularly during a relapse, Magnus and Ungley (1938) found lesions in all their 7 autopsied cases which they thought were to be regarded as atrophic processes and definitely not the end result of an inflammatory gastritis—however, all of the 9 untreated patients examined gastroscopically by Schindler and Serby (1939) presented superficial gastritis, superficial plus atrophic gastritis or patchy or diffuse atrophy.

This type of anemia occurs among rich and poor alike, among urban and rural dwellers regardless of type of occupation. Only a few cases have been reported in infancy, childhood and adolescence and the malady is very rare between twenty and thirty, but after this latter age the incidence increases rapidly up to the age of seventy, in extreme old age it is again very rare. There has come to be more than a suspicion of familial and hereditary tendencies. In the United States, England and France, more men are affected than women, but in Germany, Finland and Scandinavia the reverse seems to be true. Classical Addisonian pernicious anemia is very rare in the tropics, in the full blooded Negro anywhere the incidence is very low.

There was little significant advance in the treatment of pernicious anemia from the time that Addison described the disease in 1855 until Minot and Murphy, in 1926, announced that liver contained a principle which stim

ulated blood regeneration. These Harvard investigators, whose work was based directly upon the painstaking investigations of Whipple and his associates, who worked with dogs, found that a diet rich in liver was regularly followed by remission of the disease, without the employment of other therapeutic agents. They first reported 45 cases, but later brought the number up to 105 cases. Since that time the mortality rate for pernicious anemia has declined so uniformly in every age group that there cannot be the least doubt of the specific efficacy of the therapy. Full explanation for this magic is not yet at hand, but the classical studies of Castle and his associates have demonstrated almost beyond doubt that pernicious anemia is a deficiency disease conditioned by the lack of a specific intrinsic factor which is present in normal gastric juice but not in that of an individual with this disease. It is considered that the function of the intrinsic factor is to interact with an extrinsic factor supplied in the food to produce a hematopoietic substance active in preventing pernicious anemia in normal individuals and in checking its progress in ill individuals when given to them in some form derived from liver, kidney or brain tissue, in which it is apparently stored. Meulengracht's (1939) work suggests, but by no means proves as yet that the intrinsic factor may be secreted by the pyloric and Brunner's glands.

The practical discovery, made by Sturgis and Isaacs in 1920, that hog's stomach desiccated and defatted and taken by mouth can replace liver with equal effectiveness has been borne out by the experience of physicians throughout the world. It is believed that the intrinsic substance postulated by Castle exists in an enzyme-like form in the stomach tissue and that it acts on the muscular coat while the stomach is being ground up in the fresh state, the stomach tissue here taking the place of Castle's extrinsic or food factor, the active principle thus formed is retained in the stomach preparation and when swallowed, is rapidly absorbed and becomes at once available for use by the patient.

Miscellaneous Macrocytic (Pernicious) Anemias—Israel and Wilkinson (1936) have described 4 cases of hyperechromic megalocytic anemia characterized by normal or almost normal gastric acidity, little disturbance of the gastro intestinal tract, no involvement of the central nervous system, and lack of, or poor response to, anti anemia therapy. To this syndrome, which they consider a new entity, they have applied the title "achrestic anemia". Wauchope and Leslie Smith (1938) have reported a similar case, but it seems to me that much time and exhaustive study will be required to show that this separate classification is warranted. Alsted (1939) has reported a patient subsisting on a near starvation diet in which pernicious anemia is alleged to have arisen from lack of the extrinsic factor only. Adams and McQuarrie (1938) reported a severe functional anemia in a child, resembling pernicious anemia of adults and responding to liver therapy by complete and apparently permanent cure. Very rarely there occurs in pregnancy a type of anemia indistinguishable from classical pernicious anemia except that cord symptoms are not often seen. Untreated, the mortality is very high, but fortunately the response to liver therapy is excellent, and after remission has been thus induced relapse does not take place when the therapy is discontinued, unless pregnancy again occurs. Apparently in these cases the lack of intrinsic factor is only temporary. In most instances there is a complicating hypochromic anemia, so that iron as well as liver must be given. The present

consequence is that these rare macrocytic anemias of pregnancy are due to dietary deficiency. In a group of pregnant women in Philadelphia, to whom they deliberately maintained a deficiency in the members of the vitamin B complex, Elsom and Sample (1937) observed the occurrence of macrocytic anemias of moderate degree with some early evidences of cord involvement, but no consistent alterations in gastric acidity. The blood and clinical changes were corrected equally well by either liver extract intramuscularly or brewer's yeast by mouth (see also Tropical Macrocytic Anemia below).

Tropical Macrocytic Anemia—Since 1930, Wills and her associates have been studying a very interesting type of anemia in India. Morphologically it seems fairly closely to resemble Addisonian pernicious anemia but differs from the classical entity principally in not being associated with achlorhydria or increased serum bilirubin (indirect van den Bergh), and in manifesting no evidences of nervous system involvement. Previously thought to occur predominantly, if not exclusively, in late pregnancy, it is now believed to occur very frequently in moles also, though pregnancy does seem to predispose to an attack, the late autumn and winter rise in incidence of cases is as yet unexplained. China, the west coast of Africa, and India are the principal areas of its endemicity apparently, but Trowell (1949) has reported such cases from East Africa, Fairley *et al* (1938) from Macedonia, and the observations of Groen and Snapper (1937), and Rodriguez Molina (1939), suggest that this entity may also be encountered in Holland and in Puerto Rico. All evidence points toward this being really a food deficiency disease, but whether the missing element is merely Castle's extrinsic factor is not altogether certain—at least Wills (1939) does not seem to be currently sure. The bone marrow responds to liver stimulation as in pernicious anemia, but Wills and Evans (1938) say that response is not obtained to the more highly purified extracts. Foy and Kondi (1939) find that the Macedonian cases do respond to purified extracts but more recently Fairley (1940) has reported that the dose must be prohibitively high. Therapeutic response is also obtained to an autolyzed liver extract known as mormite (vege in the United States). Wills has shown that the active principle in this preparation is not only part of the vitamin B complex but is a substance which is water soluble, heat stable in acid medium, and not precipitated or inactivated by 80 per cent alcohol.

Sprue—The typical anemia of sprue is of the macrocytic hyperchromic "pernicious" sort and responds specifically to liver therapy, the matter is discussed in detail under Sprue.

Infestation with *Diphyllobothrium Latum*—In some instances of infestation with the fish tapeworm there arises an anemia which closely resembles that of true Addisonian pernicious anemia in symptomatology except that complete achlorhydria is not invariable and marked spinal cord involvement is rare. Sometimes improvement or cure follows expulsion of the worm. This anemia responds fully to liver therapy, if I read Castle and Minot (1936) correctly they strongly suspect it to be true pernicious anemia incidental to, and somewhat modified by, the worm infestation (see Tapeworm for full discussion).

Anemia of Hepatic Disease—Wintrobe's (1936) studies conclusively show that in cases of hepatic disease, except when there is a complicating infection or loss of blood, the anemia is morphologically very similar to that

of pernicious anemia Achlorhydria is not the rule, however, nor are there often any evidences of cord damage Wintrobe concludes that the anemia is very likely due solely to the inability of the liver to store the hematopoietic principle, the studies of Goldhamer *et al* (1934), and of Rosenberg (1936) support this hypothesis This anemia due to hepatic damage may be controlled at times by the injection of liver extract

Anemias Associated with Gastro-intestinal Pathology and Surgery—There have been some reports of one or other form of chronic dysentery, and also ulcerative colitis, associated with anemias morphologically similar to the true pernicious type, injections of liver extract in these cases can be expected to make up for the decreased absorption of the marrow stimulant Sturgis and Goldhamer (1939) list also the following conditions which may be associated with an anemia of this type total gastrectomy, extensive infiltrative carcinoma of the stomach, and various other intestinal lesions such as strictures and anastomoses, Barker and Hummel (1939) want to consider the anemia occurring in conjunction with strictures and anastomoses as a distinct disease entity

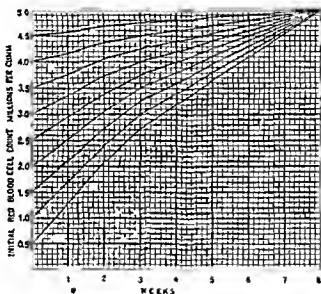
ADMINISTRATION OF LIVER AND STOMACH PREPARATIONS

At the present time throughout the world intramuscular injection of liver extract has practically entirely replaced other methods of liver therapy for the following reasons (1) Greater efficacy, patients in whom it is not possible to reach a completely normal erythrocyte count with oral methods of therapy can in most instances be brought up to normal by injection, since uneven and incomplete gastro intestinal absorption does not condition the response Likewise, in the presence of extensive liver damage with impaired storage capacity the injected extract is much more effective than that given by mouth (2) Acceptability, as compared with the oral administration of liver or stomach preparations daily, the intramuscular injections three or four times weekly in the beginning and only once weekly, or even less often, thereafter, are greatly preferred by practically all patients Since the freeing of the preparations from histamine, the anaphylactic shock type of reaction is now extremely rarely seen, the injection is usually not followed by excessive pain (3) Travel, a patient can be intensively treated by injection before departing and then need not be concerned during weeks or months of sojourning where reliable supplies of the bulky preparations for oral administration, or fresh liver, may not be obtainable (4) Cost, more hematopoietic principle can be had for the money when it is purchased as extract for injection though of course patients who cannot learn to inject themselves after a while will necessarily have frequently to meet the physician's fee (5) Speed, the patient in dire need in a severe relapse can be stimulated more quickly by injection than by oral administration in most instances

Dosage of Liver Extract Intramuscularly—This matter really comprises the three separate subjects which follow herewith

Criteria for Guidance in Dosage—There are no absolute ones really, since patients vary in response and the available commercial preparations are widely different in strength, with differences of as much as 2 cc in dosage between them in order to obtain comparable results The only safe plan is to use a reliable, clinically tested extract in dosage recommended by the manufacturer and to vary that dosage, especially not fearing to increase it

according to the reaction as indicated by frequent blood studies. Beginning two to ten days after therapy is begun the reticulocytes rise to a major peak within three to ten days, the height of which peak is inversely proportional to the level of the red cells, other things being equal. The mature red cells require some time to begin reaching the peripheral blood stream in full numbers, but usually in about two months the red cell count is within normal limits (Wintrobe, 1933 average for men 5,400,000, for women, 4,800,000)—where it should be the aim of therapy to keep it thereafter. Riddle's (1940) study of the data on 523 patients indicated that neither the reticulocytes nor the erythrocyte response is superior for the purpose of estimating the effectiveness of treatment, but since the erythrocyte count is certainly the one most often employed, I am reproducing here with Dr. Raphael Isaacs' kind permission his chart of the erythrocyte response which may be expected in adequately treated cases.



The red blood cell count, at weekly intervals for each initial red blood cell count after liver extract therapy intramuscularly. Example: With an initial red blood cell count of 1 million per cubic millimeter the count at the end of one week will be 1.7 million, at two weeks 2.4 million at fifteen days 2.5 million and so on.

A Dosage Plan—The several leaders in the study of pernicious anemia have been employing the products of different manufacturers and hence their dosages have differed, but I think it will best serve the reader's purpose if I present here only the plan of one of these groups, namely Strauss and his associates in Boston, who have for many years been employing the Solution Liver Extract Crude Lilly in the strength which contains 1 USP unit to the cubic centimeter. This extract, not being highly purified, contains many other substances present in liver besides the hematopoietically active material for pernicious anemia and is preferred by many men for this reason, the feeling being that such crude extracts are especially effective against the neurological involvements. In commencing the management of a previously untreated patient, Strauss *et al.* inject 10 cc every three or four days during the first two or three weeks, thereafter weekly injections of the same amount.

are given for the remainder of the first year. If the results have been satisfactory with regard to every aspect of the disease during the year, they feel that the 10 cc injections may then be given once in only two weeks, adequate maintenance requiring the injection of a dose at intervals of one to four weeks depending on the individual case. Weekly dosage must be at once resumed upon the reappearance of any manifestation of the disease. They have had cases in which more than 20 cc weekly was necessary to arrest the progress of spinal cord lesions, especially resistant are cases complicated by infection or arteriosclerosis.

Massive Dosage—Miller (1936) sought to determine whether patients can store, and use as their needs require, the potent hematopoietic substance if given in massive amounts during a short period of time. It seemed from the results in his 4 patients that the method might prove feasible—if it should it would of course be a boon in selected cases such as of persons obliged to travel in remote districts for protracted periods. However, Strauss and Pohle (1940) concluded as the result of treating each of 12 patients in relapse with 160 cc of Solution Liver Extract Crude Lilly intramuscularly during a period of one week that the majority of patients cannot be satisfactorily treated by the use of massive injections at long intervals. Askey (1941), upon the other hand, finds that the use of an initial large dose of 10 to 20 cc of Solution Liver Extract Purified Lilly (this 'purified' extract is considered to contain about 15 units per cc against about 1 unit per cc for the 'crude') has enabled him to obtain satisfactory control in 16 of 10 patients who were thereafter given maintenance injections at only monthly intervals. Obviously this matter of massive dosage is still in the experimental stage.

Reactions to Intramuscular Liver Injections—One might almost say that systemic reactions to these intramuscular injections do not occur, yet very occasionally a patient does develop peripheral circulatory collapse very suddenly and apparently unaccountably, though Reznikoff (1940) reports one instance in their clinic in which they were reasonably certain that the material had entered a small blood vessel. Asthmatic and other allergic reactions have also been reported a few times. These patients unfortunately have usually to be treated subsequently with liver or stomach preparations by mouth, however, Taylor and Hilger (1941) report that in 2 patients the oral administration of histaminase for two days before and on the day of injection completely prevented the systemic reactions to the parenterally administered liver extract (50 to 60 units was the daily histaminase dosage employed).

Results of Liver Extract Therapy—It is simplest to consider this subject under the following heads:

Objective Changes—Usually the skin begins to acquire color in the first week and later becomes healthy and moist in appearance. The mucous membranes share in this improvement and the tongue returns to normal in most instances. Persistent tongue lesions are felt by some observers to be associated with marked cord involvement. Isaacs, Sturgis and Smith advise painting the lesions with 1 to 2 per cent silver nitrate. Hemic murmurs, anginal symptoms, spleen palpability and edema disappear, though it should be remarked that if the patient has much cord involvement and has been bedridden, dependent edema may become more marked as he becomes ambulant. Some patients respond with a polycythemia, so that for awhile they will have a very red appearance and a blood count above normal.

Subjective Changes—The improvement in state of mind is usually rapid and marked. Appetite, physical strength and sexual power return. The distressing gastro intestinal symptoms disappear, though if there has been normal bowel activity looseness may supervene for a short time. Dizziness, blurred vision, headache, dyspnea disappear.

Effect on the Neurologic Manifestations—The effect of specific therapy upon spinal cord lesions is a point about which there has been considerable controversy, but there is a preponderance of opinion favorable to the belief expressed by Strauss *et al* (1940), of the Boston group, that adequate therapy is effective in preventing further spinal cord damage in patients who already have fairly marked lesions and in preventing the development or unfavorable progression of lesions in patients with no or minimal damage. This opinion was based upon their experience over an average period of seven years in 21 patients with advanced lesions and 64 with little or no neurological disturbances at the beginning of treatment. These workers recognize that apparent improvement in the neurologic condition may be entirely due to betterment of general health and strength, reeducation and training, and improved circulation and subsidence of edema in the spinal cord. Furthermore, that since peripheral nerves are capable of complete regeneration as long as the cell body has not degenerated, signs and symptoms referable to such peripheral nerve injury may completely disappear and lead to the impression that marked regeneration has occurred in the spinal cord. But they apparently feel that failure to check progression of a cord lesion can be blamed in any given case upon one or a combination of the following points: (a) that concomitant septic states—urinary tract infections secondary to "cold bladders," bed sores, etc.—much reduce the effectiveness of liver therapy, (b) that many reported failures are due to lack of realization that there is no more of a "standard" liver dosage in pernicious anemia than there is a standard insulin dosage in diabetes mellitus, (c) that too few cases are treated long enough before they are reported as failures.

Effect on Childbearing—Pregnancy used to be looked upon as a calamity in the life of a woman with pernicious anemia, but women are now carried through safely to the birth of healthy babies.

Effect on the Dangers of Surgery—Apparently patients on liver therapy tolerate operations very well upon the whole and are good surgical risks, but Hahn (1934), reviewing 32 cases, states his strong impression that surgical procedures definitely tend to precipitate or increase neurologic symptoms, he recommends intensification of treatment both before and after operation.

Effect on the Gastric Acidity—A few cases have been reported in which there was a return of free hydrochloric acid after adequate liver therapy, but Goldhamer (1937), reviewing the subject, doubts that these have been cases of true pernicious anemia. He does find, however, that the intrinsic factor is present in the gastric juice in induced remission.

Liver Extract by Intravenous Injection—There are preparations available for intravenous injection but their advantages over the intramuscular preparations are certainly doubtful (see, however, Sprue). Severe reactions with chill, fever, nausea and vomiting, occur very often, such preparations had best not be given at all to patients with an allergic history. Sturgis makes the point that allergic reactions to intramuscular injections are much more

likely to occur if the patient has previously been injected by the intravenous route. The Council does not accept liver extracts for intravenous administration.

Liver Extracts and Hog Stomach Preparations for Oral Administration—These preparations may be added to milk, cereals, tomato or fruit juices, or they may be given as a thick purée or in soups (heated to taste but not boiled), they may be eaten with or between meals, the entire amount at one time or in several portions throughout the day. The Council accepted (1941) preparations are the following: Solution Liver Extract-Armour, 15 cc (4 drachms) three times daily, Solution Liver Extract Oral Lederle, at least 60 cc (15 drachms) daily, Solution Liver Extract Valentine, 15 cc (4 drachms) three times daily; Liver Extract USP Oral (Stearns), 60 cc or more daily, Extralin (Liver Stomach Concentrate) Lilly, 2 Gm (4 pulvules) three times daily, Liver Extract-Abbott, 50 capsules (approximately 25 Gm) daily, Liver Extract Endo, 50 capsules (approximately 25 Gm) daily, Liver Extract Armour, 3 teaspoonfuls (3 vials) daily, Liver Extract Lilly, 3 to 6 teaspoonfuls (3 to 6 vials) daily, Liver Extract Parke, Davis and Co., 4 to 6 vials (12 to 21 Gm) daily, Ventreulin (desiccated, defatted hog stomach), 20 to 30 Gm daily.

Fresh Liver by Mouth—It is now generally agreed that the amount of fresh liver required to induce remission and maintain health in the average adult uncomplicated case of pernicious anemia is 200 to 400 Gm (wet weight) daily. It may be taken either raw or lightly cooked, provided the water employed in cooking is added in the completed dish, for the active principle is soluble. Many recipes have been made available but most patients tire in time of all of them. Falconer (1931) has described his own experience in taking raw liver in large cachets—an easy method which does away with the trouble of "lightly" cooking and also makes it possible to use the tough fibrous, and hence cheaper cow's liver. The cachets must be filled just before using else they become soggy and liable to come apart in the mouth. Kidneys are about one half, sweetbreads and brains about one third as valuable in treatment as the liver. The liver may be eaten at one or be divided between all the meals of the day. Farquharson and Graham (1930) found a broth made from beef or pork liver to be inexpensive, palatable and effective in treatment. It is made as follows: 500 Gm of liver are finely ground in a meat chopper, care being taken to save all the juice. Two glasses of water are added, and it is transferred to a fruit jar, shaken for a moment and allowed to stand for eight to twenty-four hours, if possible in a refrigerator. Finally it is heated to the boiling point, and after cooling sufficiently is strained through cheesecloth. By twisting round and round, as much fluid is expressed as possible and the total amount of fluid obtained is given to the patient every day. It may be taken cold or hot, and various flavoring agents—onions, soup powders, tomatoes—may be added if desired.

Resistance to Liver Therapy—In their original paper, Minot and Murphy indicated that infection could inhibit the effectiveness of the therapy, an observation which has been substantiated in many subsequent reports. However, we cannot yet be certain that resistance to liver therapy may not very occasionally be encountered, for a few cases have been reported in which there was progression to a typical pernicious anemia fatal termination in the absence of infection and under adequate therapy. It is a fact

worthy of note that since parenteral liver extracts have come into general use no such reports of failure have appeared in the literature—at least I have seen none

OTHER THERAPEUTIC MEASURES

Brewer's Yeast—Wintrobe (1939) has reported the employment of brewer's yeast in daily dosage of 1 to 2 Gm per kilogram of body weight with variable but in some instances quite satisfactory results in a small series of cases, he made his report however, primarily as a contribution toward further understanding of the antipernicious anemia factor rather than with the object of proposing a new type of therapy Heinle and Miller (1939) have also tried the yeast in 2 patients but did not obtain as good responses as could be had with ventriculin or with the intramuscular injection of liver extract

Nicotinic Acid—Hansen Pruss (1938) failed in his attempt to affect the course of 3 patients whom he gave full doses of this agent

Thiamine Hydrochloride—Zillhardt *et al* (1941) thought that the administration of this agent, provided it was given intramuscularly in 10 mg dosage three times weekly, had a beneficial effect on the residual neural signs and symptoms that persisted in spite of intensive antipernicious anemia therapy Their series of cases was very small, it will be interesting to see if others gain such impressions from larger series of cases

Transfusion.—Prior to the institution of liver treatment undoubtedly blood transfusion produced better and more permanent results than any other therapeutic measure It is by no means a cure but it has certainly brought many a moribund patient back to life, and in some cases it has probably been responsible for the occurrence of a remission Such cases as do respond with a remission may require anywhere from 5 to 15 transfusions before a normal blood count is approached The utmost extension of active life attainable by the use of this measure probably follows upon transfusion of 350 to 450 cc at intervals of three to five days instead of giving larger transfusions at longer intervals A number of observers still feel that the transfusion of about 500 cc of blood is the most valuable of all emergency measures Others feel that the danger of serious reactions following transfusion should always weigh against the measure if a liver preparation suitable for injection is available Davidson stated, in 1932 that he had seen 3 fatal terminations to the reaction following transfusion in the preceding two or three years, though he still felt that the measure was extremely valuable in selected cases for the relief it gives to the anoxemia from which every organ in the body is suffering

Iron, Arsenic and Hydrochloric Acid—It is believed that in pernicious anemia the breakdown products of the red cells are stored in the body and are available at once for the manufacture of hemoglobin should normal blood formation occur as the result of a natural remission or of treatment with one of the new specifics However, in a few cases the amount stored may not be sufficiently great to prevent the color index from falling to and remaining below 1.0 for a considerable period as the red cells continue to rise Under such circumstances iron is indicated (Sturgis, 1936), undoubtedly there are instances in which neither the blood count nor the hemoglobin level can be pushed up to normal without the use of the metal, but these

cases are certainly not frequently encountered. The routine employment of iron in pernicious anemia is unjustified.

It is generally agreed today that arsenic no longer has any place in the treatment of pernicious anemia.

Since the overthrow of the intestinal contamination theory of the etiology of pernicious anemia by the newer studies which have shown the disease to belong among the disorders of deficiency, there seems little rationale for the continued employment of hydrochloric acid. However, a number of physicians continue to prescribe it in doses of $\frac{1}{2}$ to 2 drachms (2-8 cc), well diluted and taken as a routine with meals, finding that flatulence and diarrhea that are not alleviated by specific therapy are kept well in check by the addition of this measure.

ANEMIAS PRIMARILY BENEFITED BY CORRECTING AN UNDERLYING DEFICIENCY

Scurvy—Anemia does not characteristically occur in the states due to vitamin deficiency of one sort or another, and when seen it is nearly always of the hypochromic microcytic type caused by insufficient intake of iron, and is correctable by the administration of iron together with the vitamin which has been ingested in insufficient quantity. A rather constant exception, however, is scurvy, in which anemia is so regularly seen as practically to constitute one of the invariable signs. It is usually of the hypochromic type but may occasionally resemble the pernicious group at least in its morphologic characteristics, achylia and cord symptoms of course not being present.

This anemia is rapidly corrected by the administration of vitamin C according to any of the methods discussed under Scurvy—at least Parsons (1933) says that it is. Castle and Minot (1936) say that it is, and the work of Mettier, Minot and Townsend (1930) seemed to leave little doubt about the matter. Josephis (1936), however, very surprisingly takes the position that in infants in the majority of instances the anemia is not affected by supplying the vitamin but is promptly cured by the administration of iron. In the adult patients of Mettier *et al* neither large doses of iron nor liver were able to accomplish the results easily achieved with vitamin C. In using iron in scurvy, Parsons warns against accompanying it with copper, which he says will destroy the vitamin.

Thyroid Deficiency—Anemia is a not infrequent finding in cretinism and myxedema, though it is not actually demonstrable so often as the pallor would lead one to expect. Usually of the hypochromic (iron deficiency) type, it may also at times have hyperchromic (pernicious) characteristics, particularly is the latter true in myxedematous individuals in whom, according to Lerman and Means (1932), the incidence of achlorhydria is high. Both iron and liver, depending upon which is indicated by the morphologic characteristics of the anemia, will induce bone marrow responses in these cases, but it seems undeniable that thyroid substance alone will slowly accomplish the same thing. Supplementing thyroid administration with one or other of the hematopoietic agents therefore seems the ideal therapy.

ANEMIAS PRIMARILY BENEFITED BY COMBATING BLOOD LOSS

This matter is treated as one of the types of iron-deficiency anemia in the earlier part of this chapter

ANEMIAS PRIMARILY BENEFITED BY COMBATING THE UNDERLYING INFECTIONS

In sepsis, which is the most frequent cause of severe acute anemia of infectious origin in the temperate zones, transfusion is employed in the several ways presented under Sepsis. In the more malignant cases of malaria in areas of great endemicity, intense anemia and hemolytic jaundice may be seen within a few days after infection occurs, but Fairley (1934) finds that in ordinary infections the chronic anemia, developing over a period of weeks to months, is far from severe. Malarial anemia, whether severe or not, is most effectively combated by use of the specific antimalarial drugs. Treatment of the very serious anemia of blackwater fever is discussed in the article on that disease. Occasionally malaria—and syphilis also, but the other infectious diseases more rarely—is followed by the acquired type of chronic hemolytic jaundice, in these instances curing the infection does not always cure the anemia. Anemia often results from the paroxysmal hemoglobinuria which occurs occasionally in syphilis, specific antisiphilitic treatment may not entirely abolish the *in vitro* evidences of hemolysis according to Castle and Minot (1936), but it usually causes disappearance of the clinical manifestations.

In states of chronic infection, most notably in tuberculosis and in the rheumatic and focal infections, a "low grade" microcytic and slightly hypochromic anemia often appears, occasionally there are evidences of bone marrow depression. Administration of iron under these conditions is a time honored custom, but I know of no controlled study of its worth before the termination of the infection. Liver stomach preparations are almost certainly of no value.

ANEMIAS PRIMARILY BENEFITED BY COMBATING CHEMICAL POISONING

A few chemical substances administered as drugs, and a larger number with which many individuals are obliged to come into contact in this industrial age, are capable of considerably depressing the hematopoietic system. Those which are of principal concern to the man in general practice are discussed elsewhere in the book (see the chapter on Poisoning, and the Index), for a consideration of the others the reader will be obliged to consult specialized works on industrial toxicology.

ANEMIAS PRIMARILY BENEFITED BY SPLENECTOMY

Congenital hemolytic anemia (icterus) is the classical entity in which splenectomy almost invariably arrests progress. The disease occurs on a familial background of the same malady and is characterized by relatively mild jaundice (which is accentuated at times of increased hemolysis), by enlargement of the spleen, chronic anemia with many erythrocytes that are microcytic and spheroidal, reticulocytosis out of proportion to the reduction in erythrocytes, increased fragility of the erythrocytes in hypotonic saline solutions, and increased urobilin in the blood. In the presence of this typical picture, splenectomy will apparently quickly and permanently put a stop to the hemolysis, though the spheroidicity of the cells persists. Whether the concept of an acquired form of hemolytic anemia of this type is admissible is at present controversial. Many observers feel that such cases are really only latent stages of the congenital disease which are diagnosed when they have become activated by some infectious, toxic or metabolic disturbance. In a recent discussion in which he champions the acquired form as a separate entity, Fowler (1941) nevertheless points out that a diagnosis of this form is not infrequently made embarrassing by the subsequent appearance of case histories or of active cases in the patient's family. The especially interested reader will likely find the review of Dameshek and Schwartz (1940) very stimulating. Of the 106 cases reported in the literature at the time they wrote, transfusions were given in 66 and were unsuccessful in arresting the disease in 22 instances, splenectomy induced arrest in 20 of the 23 cases in which it was performed. Dameshek and Schwartz consider Lederer's anemia as almost certainly the same thing as the entity under discussion, and most hematologists seem now to be in agreement that this is so.

ANEMIAS FOR WHICH THERE IS NO SATISFACTORY THERAPY

This category embraces the anemias for which no place can be found anywhere in the therapeutic classification which I have been employing in this chapter. In the hemolytic entities among them, transfusion sometimes rides the patient over until hemolysis ceases spontaneously, otherwise they really cannot be effectively treated in the present state of our knowledge. The list is short: aplastic anemia, Banti's disease (the advisability and value of splenectomy are controversial points, Davidson [1934] wants iron to be tried again in the massive doses we have learned to use in hypochromic anemias in recent years), erythroidlastic anemia of Cooley, 'target cell' anemia (and familial microcytic anemia which may ultimately prove to be a different entity), erythroblastosis foetalis, leuko-erythroidlastic anemia, sickle-cell anemia, anemia of toxic nephritis (see Nephritis), anemias resulting from radium or roentgen ray injury, anemia in the leukemias, Hodgkin's disease and carcinomatosis of the bones, anemias of Albers-Schönberg's, Minkowski's, Gaucher's, Niemann-Pick's, and Schüller-Christian's diseases.

BLOOD DISTURBANCES OTHER THAN THE ANEMIAS

BLOOD DISTURBANCES OTHER THAN THE ANEMIAS

ERYTHREMIA

(Polycythemia Rubra Vera)

Erythremia is a rare disease occurring in all races, in either sex, and usually after the age of fifty. The cause is unknown but in some of the cases, usually the milder ones, there is a distinct familial background. The patient complains of lassitude, weakness, loss of weight, dizziness, tinnitus, congestive sensations especially in the hands, dyspnea, gastro intestinal disturbances, and often severe headache, muscular spasms and neuralgias and paresthesias of the extremities. There is a pronounced hemorrhagic tendency in the disease. Examination reveals red cyanosis of the face and hands (though it is said that an occasional patient may be actually pale, but it is doubtful if any victim of this disease is at all times pale) a greatly enlarged spleen in the majority of instances, congested conjunctivae, and a typical blood picture. The red cells are increased to from 8,000,000 to 14,000,000, there are a great many immature cells present and differences in staining are marked, the number of white cells is usually two or three times the normal and the platelets are also sometimes much increased, hemoglobin is more than 100 per cent. Although the total blood volume is much increased, the increase in plasma is not in direct proportion to that in cells, with the result that viscosity is much increased. Despite the diffuse capillary dilatation that is known to occur in this disease, it is quite surprising that the heart rate is not greatly increased and the organ itself hypertrophied more often than is actually the case. Kidney function is often impaired and both blood pressure and the basal metabolic rate sometimes increased.

Dameshek and Henstell (1940) feel that erythremia is probably more common, particularly among Jews, than is ordinarily suspected, and that it may masquerade for months or years under such guises as neurasthenia, migraine, cardiovascular renal disease, gastro intestinal disorders, and peripheral vascular disease. This is a fatal malady but there are remissions in most cases. Death seldom occurs under five years and may be deferred as long as twenty years, though this is unusual, some of the cases of long standing seem to merge into anemic, leukemic or thrombocytopenic states. If death is directly attributable to the erythremia, it is consequent upon increased sluggishness of the circulation or due to a vascular catastrophe, such as hemorrhage or thrombosis.

THERAPY

Phenylhydrazine Hydrochloride.—In 1924, Owen reported a case in which he had successfully used this drug, and in 1925 he brought the number of cases up to 5. These patients were all benefited, as was evidenced by a uniform decrease of the hemoglobin and red cells, a great improvement in all the symptoms, and a reduction in blood pressure of the three individuals who had hypertension. Since that time a large number of case reports has

appeared in the literature, in most of which the drug had been used very successfully. The dosage plan advocated by Owen is the one usually followed (a) treatment may be safely begun in most instances with 3 grains (0.2 Gm) daily for three or four days then $1\frac{1}{2}$ grains (0.1 Gm) daily until the leukocytes increase in number or the hemoglobin falls below 100 per cent (b) with the advent of either of these two occurrences, usually after several weeks the $1\frac{1}{2}$ grain dose may be given every second or third day, or the drug may be stopped altogether, resuming medication when the hemoglobin and red cells rise or the leukocytes begin to fall, (c) gradually the interval between doses can be lengthened with the hope of ultimately maintaining the blood count within normal limits on $1\frac{1}{2}$ grains once a week. However, the experimental studies of Giffin and Allen some years ago indicated that the leukocytosis cannot always be taken as a reliable index for therapy since the increase in the white cell count may be at times predominantly due to the breaking down of red cells and at other times to stimulation of the hematopoietic system, it very doubtfully indicates damage to liver cells. In Stealy's (1932) valuable experience of seven and one-half years' medication of 1 patient, he several times felt justified in continuing with the drug through a period of extreme leukocytosis unaccompanied by much decrease in the red cell count. His dosage was a total of 2.1 Gm (about 32 grains) of the drug divided into daily doses of 0.1 Gm ($1\frac{1}{2}$ grains) each, after each such dosing period there was an interval of one and one half months without drug treatment. Instances of acquired tolerance to the drug, requiring increase in dosage, have been reported, but in Stealy's experience such periods of tolerance were always temporary.

It has been suspected that injury to the liver or kidneys might result either from the drug itself or from excess hemolysis but clear-cut proof of this has not been forthcoming. Certainly its use should be carefully checked by studies of the blood and not be allowed to depend upon its effect upon other symptoms such as the pain in an extremity, rapid hemolysis may be fatal of course. Kennedy (1934) gave his patient 4 short courses of treatment without untoward effect, but the fifth produced a severe hemolytic crisis, which he successfully combated by blood transfusion and the administration of liver extract. Giffin and Conner feel, from a review of the literature and their own experience, that (a) patients should be kept ambulatory as much as possible, (b) advanced cases confined to bed should not receive the drug, and (c) it should be given with greatest possible caution to those above sixty years of age, to patients with marked arteriosclerosis, and to those who manifest evidence of thrombosis or advanced visceral injury.

Acetylphenylhydrazine—Stone *et al* (1933) used this drug satisfactorily in 2 cases over periods of seven and four and one half years, respectively, and believed it to be superior to the above preparation because it is probably less toxic and the dosage is easier to regulate. The drug seems now to have become generally the one of choice. McAlpin and Smith (1938), who have treated 14 cases, start their patients on $1\frac{1}{2}$ grains (0.1 Gm) daily for two or three days then a few rest days, a blood count, and then start over again. This is continued for three or four weeks, then if necessary, the dose is gradually increased to 4, 5, or rarely 6 doses per week. If there is any drop in erythrocytes and hemoglobin the drug is stopped at once for a week or more until regeneration to a safe level has occurred. The attempt must of course

be made to find the individual tolerance of each patient, but this is far from a simple thing to do because there seems to be a cumulative effect difficult to estimate. Reznikoff (1940) says that some patients can be kept with a fairly normal blood count for a long period on only 0.1 Gm. once a week while others will require that amount every other day. In addition to a sudden drop in the red cell count, McAlpin and Smith list the following as signs of overactions of the drug: jaundice, gastro-intestinal symptoms, and fever (which alone acted as a danger signal in one of their cases).

Potassium Arsenite—Forkner, Scott and Wu (1933) obtained distinct improvement in all of their 6 patients by saturating with Fowler's solution in the conventional way except that they liked to reach 20 minims (1.2 cc.) three times daily instead of stopping at 10 minims as is usual in other conditions.

Roentgen Therapy—Irradiation of the spleen is contraindicated since there are a number of cases on record in which the procedure has increased the severity of the disease, irradiation of the long bones however seems to be of some value, improvement taking place in most cases. The usual practice is to apply a rather large dose to the long bones, the scapula, the sternum, the pelvis, and eventually the vertebral column, or the ribs. The effect is temporary, and Minot says that as time goes on the therapy often becomes ineffective. A considerable, or even a sudden inconsiderable, decrease in the leukocytes of the circulating blood indicates that the leukocyte forming tissue of the bone marrow is being injured and calls for immediate cessation of the treatment. Hunter (1930), following the earlier European observers, believes general irradiation to be the method of choice. Acting upon the assumption that polycythemia may be due to an excess of the hematopoietic factor which, through its absence, causes a reversed picture in pernicious anemia, Anderson *et al.* (1938) applied roentgen therapy to the pylorus and duodenum in a single patient and reported good results, however, Stenstrom *et al.* (1940) have failed to induce a remission with the same treatment in any of their four patients.

Venesection and Reduced Iron Intake—Frequent extensive bloodletting affords temporary relief in most patients. Stephens and Kaltreider (1937), in a careful study of 5 patients, found that by the repeated and systematic letting of about 500 cc. of blood at intervals of from one to several days it was possible to reduce the volume of the red blood cells to or slightly below normal, there was a corresponding decrease in the number of red blood cells and hemoglobin and a reduction in the blood viscosity, blood volume and blood velocity to approximately normal levels. Hematologic improvement was usually accompanied by marked relief of symptoms and reduction in the size of the spleen. In 4 of the 5 patients there were remissions of from eight months' to two years' duration without further treatment. These observers feel that venesection compares favorably with other types of treatment, but Naegeli (1934) thinks it not without danger from the standpoint of inciting thrombosis, and justified only to afford relief when the feeling of pressure in the bend becomes unbearable, however, many men now think highly of venesection. Dameshek and Henstell (1940) aim at producing a state of chronic hypochromic anemia so that the blood viscosity, total blood volume, red cell volume, and red cell mass will all be reduced. Their method consists in venesections of 500 cc. twice a week until hemo-

globin is reduced to 80 or 85 per cent, red cells to 5 or 5.5 millions, and the hematocrit reading to between 42 and 45 per cent. They say this usually requires six to eight venesections. Thereafter the patient is kept on a diet low in iron, which requires avoidance of red meat, meat soups, liver, eggs, rye bread and brown cereals (protein is derived from fowl once a week, fish twice a week, cheese, milk and legumes). Very good results are reported with this regimen.

Holbrook (1911), of Milwaukee, reporting an instance in his series of 10 cases in which the patient felt decidedly worse for about a month following one of the bloodlettings, interestingly raises the point that a marked discrepancy between the red cell count and the blood viscosity might serve as a contraindication to venesection, for this patient had a blood viscosity of only 5.5 with a count of 8,000,000 when a viscosity of 8 would have been normal.

LEUKEMIA

Leukemia is a relatively rare and always fatal disease of unknown etiology characterized chiefly by the presence in the blood stream of large numbers of abnormal white cells, though in some of the cases there occur at times aleukemic phases in which the white count is found to be below normal. Leukemia is a disease of fowls and the lower mammals as well as of man. It occurs more frequently in males than in females, a familial tendency has not been proved.

Acute myelogenous and lymphogenous leukemia occurs usually in children and nearly always except for the monocytic form, in individuals under twenty-five years of age. It is rapidly fatal, death occurring usually within a few days to a few weeks at most. The attack is often superimposed upon an acute infection such as tonsillitis or a furuncle. There is malaise, headache, high fever, bone pain, extreme prostration and a rapidly increasing pallor. Ulcerative lesions appear in the mouth and throat, and marked enlargement of the regional lymph nodes of the neck occurs very rapidly, lymph nodes elsewhere in the body, and also the spleen are slightly enlarged. Bleeding occurs both externally and internally from the mucous membranes and sometimes also in the fundus of the eye, hemorrhages of the skin are almost the rule and various types of vesicular eruptions are frequently seen. There is very rapid decrease in the number of red cells and the amount of hemoglobin, and marked platelet reduction at the same time the number of white cells is mounting though it rarely attains the great height seen in the chronic form of the disease. Immature red cells are also present in large numbers. Lymphocytes and lymphoblasts usually constitute more than 90 per cent of the white cells but sometimes myeloblasts predominate, it is only in recent years that the monocytic form of blood picture is being reported, a few cases of acute eosinophilic leukemia have been described.

Chronic leukemia is insidious in its onset, but usually causes death from anemic exhaustion, hemorrhage, or intercurrent infectious disease, for which the resistance is much lowered, in about three years, a few cases last as

long as ten years and a rare case even longer, but true recovery never occurs. The most prominent symptoms are marked enlargement of the spleen, which causes great discomfort, pallor, dyspnea, dizziness, palpitation, bone sensitiveness, gastro intestinal disturbances, loss of weight, and progressive weakness. Hemorrhage and fever are much later in their appearance than in the acute form of the disease. In lymphogenous leukemia the spleen is not usually much enlarged but there is marked general enlargement of the lymphatic glands, a finding which is quite unusual in the myelogenous type, even the tonsils and the Peyer's patches in the intestine show proliferative changes. The glands are at no time inflammatory. The blood is pale in color, with a low red count and much reduced hemoglobin. Immature and abnormal red cells are present. The white count is rarely increased more than to 200,000 and consists almost exclusively of pathologic lymphocytes; the platelets are always reduced. In the myelogenous type of the disease there is an increase in white cells to from 100,000 to 1,000,000 or more. Polymorphonuclear, eosinophilic and basophilic leukocytes are relatively and absolutely increased, the lymphocytes are relatively reduced but absolutely increased and immature cells from the bone marrow are present. Blood platelets usually abnormal in appearance, are initially increased but finally decreased in number. Neutrophilic myelocytes usually predominate, but monocytic and eosinophilic cases are seen, plasma cell cases have been described, and there are other types difficult to classify. Bone-marrow changes have been observed to precede the positive leukemic manifestations in the peripheral blood indicating that bone marrow biopsy might be advisable in all doubtful cases. Chronic myelogenous leukemia occurs most often in individuals between twenty five and forty five years of age, chronic lymphogenous leukemia in those between forty five and sixty.

In 1935, Schwab and Weiss called attention to the relative frequency of neurologic complications in both acute and chronic leukemias—a fact not much stressed before that time.

THERAPY

Acute Leukemia—There is nothing to describe.

Chronic Leukemia—*Irradiation*—Radium is sometimes applied over the splenic area but roentgen therapy is the more generally accepted method. However, there is certainly still great diversity of opinion with regard to technic, some advocating that attention be directed to the spleen and enlarged nodes only, others irradiating only the chest or trunk, and others practicing irradiation of the entire body. It seems to be the consensus that irradiation increases the comfort of the patient in most instances and often enables him to remain active longer than without it, but few observers now feel that the length of his survival is much increased. The details of this type of therapy cannot be described here, the reader is referred to the recent paper of Dowdy and Lawrence (1941).

The employment of radioactive phosphorus by Lawrence *et al* (1939), and Warren (1940), is still entirely experimental.

Benzene (Benzol)—The toxic action of this agent has caused it to be abandoned—at least I do not know of any clinic in this country in which it is still being used.

Arsenic—In 1931, Forkner and Scott reawakened interest in the use of Fowler's solution by their report of good results. Forkner (1940) has recently stated that he begins with 3 or 4 minims (0.2 to 0.3 cc) thrice daily in a heverage after meals and gradually increases about a minim a day until 8, 10 or even 15 minims are being taken three times daily. The leukocyte count is said to begin dropping on about the twelfth day with symptomatic remission following shortly. The dose is decreased a minim a day when the leukocyte count is about normal, and when return to 4 or 5 minims three times daily has been accomplished the patient is held at this level. Forkner says that a remission of many months can often be maintained in this way but warns that the drug must be reduced *slowly* as above stated to accomplish this. Arsenic is much used but not all observers feel that it is often of value, for example, Wintrobe and Hasenbush (1939) found it of no value in a small group of lymphogenous cases and of less value than irradiation in myelogenous cases. In their experience the toxic symptoms following arsenic were greater than those following x ray. Kandel and LeRoy (1937) found it difficult to judge whether the likelihood of inducing hyperkeratosis, neuritis, herpes zoster, and possibly cirrhosis with arsenic outweighed its beneficial effect in the disease. The arsphenamines intravenously are definitely dangerous in leukemia, a number of acute deaths have been reported.

Other Agents—On the basis of the alleged causative role of amidopyrine (pyramidon) in agranulocytosis, Terry and Sanders (1934) treated a case of chronic leukemia intensively with phenobarbital (luminal) and amidopyrine. Speidel (1937) has also treated a case with amidopyrine alone. Both report good results, but I doubt the logic of this treatment.

Lucia (1935) reported good palliative results in a few cases in which he injected intravenously a freshly prepared 1 per cent solution of potassium antimonyl tartrate, in doses of 2, 3, and 5 cc on alternate days in series of four to eleven injections.

Transfusion has often been effectively employed to offset the tendency toward hemorrhage and to relieve the anemia temporarily until it has been possible to irradiate the patient sufficiently to produce results. The intramedullary (sternal) transfusion of normal human bone marrow, as practiced by Morrison and Samwick (1940), is still in the experimental stage. Davis and Fitz Hugh (1939) found that liver therapy has no effect on the anemia of leukemia. Splenectomy is nearly always fatal.

For many years it has been known that intercurrent infections during the course of leukemia are accompanied by a fall in the number of leukocytes. Gamble treated 2 cases by the therapeutic production of malaria. In each of these cases there was a prompt fall in leukocytes to half the previous number. Following the termination of the paroxysms, however, the leukocytes rose, in three and six days respectively, to approximately their previous level. Lucchini had better results in his case: the leukocytes fell from 250 000 to 4400 after twelve paroxysms, and at the end of the reported observation of the case, six weeks after paroxysms were stopped with quinine, the blood count was leukocytes, 5800, erythrocytes, 4 400 000, hemoglobin, 52 per cent, the differential count was said to be normal.

HODGKIN'S DISEASE

Hodgkin's disease is an affection of the lymph nodes of unknown etiology and invariably fatal termination. Males are more frequently affected than females, the majority of cases in either sex occurring between the ages of fifteen and thirty five. In the usual form of the disease the patient notices a gradual, nonpainful, discrete enlargement of glands in the cervical region in the beginning the enlargement may be unilateral but both sides are almost invariably involved ultimately. In most cases the axillary and then the inguinal glands, and finally both superficial and deep glands all over the body, become involved. Moderate enlargement of the spleen, and often an increase in the size of the liver, take place. The patient loses weight and becomes cachectic. General pruritus of a very severe and persistent type is a not infrequent early symptom. A peculiar feature of the disease is the frequent alternating febrile and afebrile periods. The enlargement of cervical, mediastinal, retroperitoneal or mesenteric groups of nodes may cause symptoms which make the picture a very complex one, involvement of the vertebrae and the cord, when this occurs, is usually a very late manifestation. Initial involvement of the retroperitoneal nodes without subsequent mediastinal or peripheral manifestations is infrequent. The disease usually terminates in death within two to three years, though many patients have lived a few years longer than this, cachexia and profound anemia (usually of the hypochromic, microcytic type), mechanical obstruction of one sort or another, or intercurrent infection is usually the immediate cause.

I have presented briefly here only the most usual type of which there are numerous variations—Middleton (1937) very aptly writes of the clinical 'caprices' of this disease. Histologic examination of an excised node (Meyer, 1911, says that nodes from sites other than the groin are most apt to show affection by the primary disease rather than mere lymphadenitis) shows very definite alterations in structure which cannot be described here for obvious reasons, likewise, the blood picture in the various types of Hodgkin's disease is a topic that is still in a state of too great confusion to warrant its discussion in a book of this sort.

Recently, Wise and Poston (1940), following earlier studies of the same group of investigators at Duke University, have reported the coexistence of brucella infection and Hodgkin's disease in 14 consecutive cases in which *B. melitensis* was isolated from blood and lymph node cultures, while failing to isolate the organism from a much larger group of patients with lymph node affections other than Hodgkin's. Forhus and Gunter (1941), also at Duke, have isolated *B. melitensis* and *B. suis* from a variety of tissues at 5 consecutive autopsies on cases of typical Hodgkin's disease. Gambrell (1941) points out that it is very strange that the organism should not be *B. abortus*, which is the one most commonly found in this country, she has not been able to obtain positive evidence of brucella infection in any Hodgkin's cases at Emory University and in 2 autopsies failed to confirm the findings of Forhus and Gunter. So this extremely interesting new approach is at present still merely extremely interesting.

Malpighi (1628-1694) gave the first vague account of this disease, which was fully described by Thomas Hodgkin in 1832. Evidence is accumulating (Steiner, 1941) that Gordon's test, if positive, is of considerable supportive aid in the diagnosis of Hodgkin's disease.

has been studied sufficiently so that its existence as an entity may be granted without reservation, and it is this type alone with which this present article concerns itself. Incidentally, however, one should mention the interesting infectious agranulocytosis of cats, with which Lawrence *et al* (1940) have been working though it is not known to bear any relationship to the human disease. Classical human agranulocytosis was first described by Schultz, in 1922, before which time it had doubtfully existed, mounting then rapidly in incidence to reach a rather alarming peak just before the discovery of its causative agent, in 1933, it has since so quickly declined that those who rather rapidly became authorities on the subject now rarely have opportunity to see a case. The rise was all the more "alarming" in that many of the victims were physicians and their families, nurses, technicians and others directly connected with the profession, it is predominantly a disease of adults of the middle and upper (and therefore in America almost exclusively white) classes. The onset and course are often of dramatic suddenness and despatch collapse, chill, fever, red throat or ulcerative stomatitis, and possibly ulcerative (without the usual inflammatory reactions) and gangrenous lesions elsewhere throughout the body, sometimes jaundice, very occasionally a slightly enlarged spleen, marked leukopenia and granulocytopenia without notable anemia, stupor and death. Meningitic symptoms have been described in 1 case (Goadby *et al*, 1935). Sepsis develops in many patients before the end the organisms being the normal inhabitants of the oral cavity or lower intestine, but it would seem that complete absence of granular cells for seven days, more or less, is in itself incompatible with life for some patients die before ulceration, necrosis and sepsis have developed. Though monocytes may sometimes be present in the peripheral blood in abnormally high percentages (Reznikoff, 1938, feels that persistent monocytosis is evidence of good prognosis) the majority of the white cells are usually adult lymphocytes. Marked thrombopenia and a consequent bleeding tendency is probably rarely seen in cases which are unequivocally primary granulocytopenia. The findings of Fitz Hugh and Krumhaar (1932), corroborated by those of Custer (1935) and Darling *et al* (1936), established the primary fault as a maturation arrest of the myeloid (white cell) series in the bone marrow analogous to the erythroblast arrest in pernicious anemia.

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General Therapy.—It is felt to be important that the patient carry out a regimen as for tuberculosis, with rest and fresh air, moderate exposure to sunshine, and a good nutritious diet—"other than that," says Craver, "there is not much to be done."

Irradiation.—The application of radium or x rays to the enlarged nodes causes a great reduction in their size and consequently leads to considerable amelioration of symptoms. The effect is always temporary, however, and the response to subsequent courses of treatment is less satisfactory. Finally, a point is reached at which there is no response at all. It is quite doubtful whether these agents really extend the length of the patient's life, though there is no denying that they make his existence much more comfortable, it is possible to match every case of exceptionally long survival under irradiation with a case given no treatment at all. Meyer (1931), while by no means decrying the use of the x ray, nevertheless warns that atelectasis and bronchial reaction and hypersecretion may follow irradiation of the mediastinal masses.

Arsenic—This is the only drug of any "specific" value, the dosage scheme of Forkner (see Leukemia) sufficing here also. The nodes sometimes recede temporarily under this treatment, but, as in the case of irradiation, the ultimate course of the disease is not affected. It does not seem that the response is obtained nearly so often with arsenic as it is with irradiation.

Treatment of Anemia—It is the consensus that transfusion is often of value in improving the patient's general physical condition, iron is also often helpful. In the rare case, such as that of Townsend and Braunstein (1939), in which the anemia is of the hyperchromic, macrocytic type, liver extract is of course indicated.

Surgery.—It is now generally conceded that the removal of glands by operation is inadvisable in the vast majority of instances. Even the removal of a single gland for purposes of diagnosis should be postponed until it is certain that the procedure is absolutely necessary.

AGRANULOCYTOSIS

(Agranulocytic Angina, Malignant Neutropenia, Primary Granulocytopenia)

It does not seem that anyone has fully classified the varieties of agranulocytosis, but the following seem to have attained at least tentative rank as distinctive entities: (a) the low grade chronic type first described by Roberts and Kracke, in 1931, and referred to again by Kracke as recently as 1938, (b) the type, either acute or chronic in its course, which seems to be associated with excessive splenic lysis of granulocytes and is apparently corrected by splenectomy—first reported by Wiseman and Doan, in 1939, (c) the unusual "cyclic" cases in which granulocytopenic episodes, with spontaneous recovery, are alleged to recur at somewhat regular intervals, and (d) the type characterized by acute onset, brief fulminating course, and death in the majority of instances. It is the last of these types only which

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The classical experience and experiments of Madison and Squier, reported in 1933 substantiate the statement made above that the causative agent has been found. In their series of 14 consecutive cases there was a history in each instance of amidopyrine (pyramidon) having been taken immediately prior to the clinical discovery of granulocytopenia in 7 cases combined with a barbiturate and in 7 cases alone or in combination with drugs other than barbiturates. Five of these patients were being treated in the hospital for other conditions in the handling of which amidopyrine was being employed, when the agranulocytosis appeared. In the 9 instances in which the drug was withheld there were only 2 deaths (the mortality was 100 per cent in the remainder of the group), both patients having been moribund when the diagnosis was made. One patient, who had had his initial attack eighteen months previously and who had been in a state of complete remission for ten months, took 5 grains (0.3 Gm.) amidopyrine in the evening—within three hours he had a chill, in the morning symptoms had returned and he was found to be almost agranulocytic. Another patient whose first attack had developed

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everyone who ingests the drug to develop the disease than to expect all who inhale ragweed pollen to have fall hay fever. Holten (1937), borrowing Quick's hypothesis regarding cinchophen hepatitis, feels that profitable experimentation might be begun upon the assumption that the granulocytopenia is an Arthus phenomenon localized to the leukopoietic part of the bone marrow.

(b) That no contact with the drug can be demonstrated in some instances is not an insuperable objection. In the first place, it is as a matter of fact very difficult to prove that an individual has not taken the drug in some form. In the second place, no one contends that this drug alone is capable of producing the syndrome, the organic arsenicals, certain of the gold salts, dimetophenol, acetphenetidin (phenacetin), neostibosan, the sulfonamides and possibly several other drugs have been known to do so occasionally. And if the ailment is allergic the patient may be responsive to some allergen quite outside this group of drugs—who knows? But the important point is that some individuals do respond allergically to amidopyrine with an attack of primary granulocytopenia. And third, granting that the patient may recover during the administration of the drug (beware of faulty diagnoses!), what of it, in view of the remarks just set down above and of the present limitations of our understanding of allergy?

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It is probable that no one has had sufficient experience in the treatment of primary granulocytopenia to warrant us in considering his findings of statistical value, what follows in this place is therefore merely a report of methods that have been used. Kracke (1938) makes the point, and Reznikoff (1939) and doubtless many others concur, that since agranulocytosis is an emergency illness and these remedial measures are not harmful their use is justified even though we lack convincing evidence of their worth. However, it seems to me important to note Madison's feeling that if diagnosis is made before granulocytes have been absent from the peripheral circulation more than twenty-four hours, treatment may be undertaken with good hope of success provided there do not happen to be virulent organisms in the nasal, pharyngeal or other mucous membranes. Indeed, he thinks spontaneous recovery quite likely to take place under these circumstances, in the 1 case of this sort in which he refrained from employing any therapeutic measures the patient got well. In 2 patients who had high monocyte counts, which he looks upon as a good prognostic sign, Reznikoff also employed no therapeutic agents and recovery occurred.

General supportive measures are of course indicated, particularly cardiac stimulation and the supplying of adequate nourishment in easily assimilable form. Griffith (1932) records a case in which he felt that the forcing of fluids through a Jutte tube passed through the nose into the stomach and left in place for seven days, by means of which 120 to 130 ounces (3600 to 3900 cc.) of a high carbohydrate liquid diet (not specified but I should think that 10 to 15 per cent glucose solution would be satisfactory) were given resulted in overcoming the dehydration, and causing good kidney function, without disturbing the hematopoietic system or overloading the heart by fluids introduced intravenously. Isolation, in the attempt to prevent infection, would certainly seem to be a rational procedure.

Discontinuance of the Use of Amidopyrine and Related Drugs—This drug is in use not only under its own name but in many disguised forms as

well The following is the most complete list that I have been able to obtain of the American proprietary preparations that did or do contain amidopyrine, or a compound of it, or that are capable of yielding it in the body in such form as would carry the potentiality of causing primary granulocytopenia The list was brought up to date by Kracke, in 1938, from it I have deleted two preparations, 'antabs' and "analga," which the manufacturers claim do not contain amidopyrine, and "allonal," in which acetphenetidn is said to have replaced amidopyrine in January, 1939, to it I have added "causalin," which is said to contain amidopyrine and has been reported in association with attacks of agranulocytosis by Jackson (1938), Dardinski and Lyddane (1939), and McGovern (1940) The list does not include many of the large group of patent" or secret formula medicines

Alphebin	Benzedo compound	Midol
Amarbital	Causalin	Mylan
Amidol	Cibalgin	Neonal compound
Am do-neonal	Cinchopyrine	Neurodyne
Amidonine	Compral	Nod
Amidophen	Cronal	Novaldin (novalgin)
Amidos	Dymen	Optalidon
Amidotal compound	Dysco	Peralga
Amifeine	Eu med	Phenamidol
Aminol	Gardan	Phen-amidol
Am phen al	Gynalgos	Phenopyrine
Ampydin	Hexin	Pyramidon
Amlytal compound	Iprat amidopyrine	Pyraminal
Baramid	Kalms	Seeqit
Barb amid	Lumodrin	Yeast vite

Pentnucleotide—The hypothesis of leukocyte disintegration products as stimulants of leukocyte production is enticing but it is not certain that very much of practical value has accrued from it Pentnucleotide therapy has been used with varying success by many physicians all over the world Its chief champions are still those who introduced it—Jackson and associates—who now recommend that 40 cc be given each day intramuscularly Unfortunately there are sometimes fairly severe systemic reactions, which may perhaps be avoided by beginning with lower dosage Madison believes that it may be wise to continue administration at two to four week intervals for some time following recovery

Adenine Sulfate—Reznikoff (1933) reported the use of this drug with favorable results in cases that were not severely complicated The suggested dosage was 15 grains (1 Gm) of adenine sulfate boiled in 35 to 40 cc of physiologic saline solution given warm, intravenously, three times a day for at least three days

Blood Transfusion—Since no technically satisfactory method of transfusing leukocytes alone is at present available, whole blood transfusions are resorted to, but it must be admitted that the rationale of the method is open to legitimate doubt since the transfusion of 500 cc of blood can theoretically only raise the leukocyte content of the recipient's body by 6 per cent However, Dorn feels that transfusion is a rational procedure on the basis of its nucleic acid content Madison feels that it is definitely indicated, especially if there is severe infection of the membranes, and particularly if there is a bacteremia Witts (1936), in England believes it not to be indicated and

Jackson (1935) writes. "Personally I am decidedly against transfusions in this disease", but Reznikoff (1939) feels that transfusions are not likely to harm the patient. Those who employ them usually give 250 to 500 cc daily or on alternate days until the leukocyte rise is well advanced. Harkins (1931) felt that the blood of a recovered patient was of especial value in the 1 case in which he used it, Kracke also prefers such blood when it is available.

Leukocytic Cream—Strumia (1934) gives daily intramuscular injections of leukocytic cream made from the blood of a donor by a special method of his devising. Fitz Hugh (1935) says the injections are harmless and may be helpful, though they were not of benefit in his personal experience.

Liver.—Liver has been used as in macrocytic anemias. I think it significant that when von Bonsdorff reported 2 liver treated cases in 1934 he was enthusiastic, but the mood was not sustained when his series had increased to 15 cases in 1936. Of the 4 liver treated patients in Jackson and Parker's series they remark succinctly "all died." Herndon (1935) has reported granulocytopenia as a terminal event in a patient undergoing vigorous liver therapy for pernicious anemia, on the other hand, Das Gupta and Witts (1937) report recovery of a "chronic" case treated with liver extract.

Yellow Bone Marrow—Some years ago there began to be talk of the use of this agent at the Mayo Clinic, and in 1938, Watkins and Giffin read, but so far as I know did not publish, a paper in which it was said that 200 to 400 grains (1 patient took as high as 800 grains) daily of the marrow was employed in 24 patients during 20 attacks, the number of attacks in which they felt adequate dosage was administered was only 21, recovery occurring in 10 instances. The concentrated preparation (Armour), prepared and used by Marberg and Wiles (1938) in a small series of cases, is given in a dose of 1 to 5 cc three times daily by mouth.

Nonspecific Proteins—Attempts to stimulate leukocytosis through such measures as the intramuscular injection of turpentine, milk, or bacterial products are illogical since in the presence of maturation arrest in the marrow there are no leukocytes to be mobilized. One of Jackson's cases developed in the midst of an attack of boils.

Roentgen Therapy—X ray in this disease is certainly a two-edged sword, as pointed out by a number of observers and there is no escaping the fact that the difference between the dose which will stimulate the hematopoietic tissues and that which will destroy them cannot be accurately known to roentgenologists since it most probably varies widely from individual to individual, therefore the assumption upon which therapy is based, namely, that there is a fixed stimulatory threshold below which primary destruction of cells does not precede regeneration, is—well, assumption. Doan, indeed, believes that such good results as may be obtained are directly chargeable to destruction of myeloid foci with a liberation of autogenous nucleotide and resultant initiation of maturation, Madison concurs in this view, but the only 2 x ray treated cases which he has seen terminated fatally.

Local Therapy.—The usual treatment for severe stomatitis is considered to be indicated by most observers (see methods under Stomatitis), but some think that the continuous swabbing of the lesions with various antiseptic solutions serves only to disturb the patient needlessly. Madison believes that the local application of antiviral is probably of considerable value. Griffith made daily applications of an erythematous dose of ultraviolet light to lesions

in which streptococci predominated, hoping for the same good result some times obtained in erysipelas. As a matter of nursing detail the utmost attempts to maintain asepsis and to prevent cross contamination are mandatory.

THE PURPURAS

Nowhere in medicine today is there greater confusion than in this subject of the purpuras, the reason being of course our lack of knowledge. I am sure the present article will not satisfy specialists in this field, it certainly does not satisfy me, but it represents the best I have been able to do within the limitations of space and time and my own inadequate grasp of the subject.

Thrombocytopenic Purpura (Purpura Haemorrhagica)—This entity, which is probably the one with which Werlbos was dealing in 1735, is pre-eminently a disease of the young, though no age is exempt, females are more often affected than males. There is marked diminution in the number of circulating blood platelets, which may be brought out by repeated counts if a single one does not demonstrate it, prolonged bleeding time and little or no clot retractility, normal or nearly normal coagulation time, evidences of normal blood regeneration, and a positive constrictor or armband test (Rumpel Leede). The spleen is usually not palpable. Spontaneous capillary hemorrhages may occur into any of the tissues, bleeding from the uterus, nose and mouth, and into the retina being the most common. The cutaneous hemorrhages vary from a few petechiae to extensive ecchymoses. Hemorrhage into basal ganglia may cause fever, mental disturbances, convulsions, cerebral hemorrhage. The bleeding often begins without warning and persists intermittently for days or weeks, death resulting in severe cases from exsanguination. A chronic form of the disease is recognized, which does not develop from the acute form but is chronic throughout. These patients give a history of having bruised and bled easily for many years before the onset of the attack in which diagnosis is made from the blood findings. Such individuals bleed intermittently during a number of years, some dying and others apparently recovering completely. Cases have been reported in which a rapid fall in platelets and the appearance of purpura were associated with menstruation, with remissions between and recurrence with the succeeding periods, indeed it would seem from the work of Puhle (1939) that in many normal women there is a cyclical variation in the number of platelets in regular relation to the menstrual cycle. Goldhurgh and Gouley (1940) and Snaith (1940), have described cases in which menorrhagia was the only or the first symptom of thrombopenic purpura. Two interesting cases illustrative of congenital purpura are reported by Davidson (1937), and by Bernstein *et al* (1939) in one, a purpuric infant was born to a mother whose platelet count had always been low during the several years after removal of her spleen because of purpura; in the other, a normal infant was born to a mother whose platelet count became normal after removal of her spleen during the pregnancy.

The clinical manifestations in thrombopenic purpura are currently believed to be due to an idiopathic reduction in the number of platelets, but perhaps

the fault may lie not so much in a quantitative as in a qualitative alteration in these elements. Conversely, abnormal permeability of the capillaries is held jointly responsible in some cases by some observers (Madison and Squier, 1940), the recent findings of Leonard and Falconer (1941), studying the experimental condition in the guinea pig, somewhat support this position. A hypothetical toxin, acting upon either the platelets or the capillary walls, has been postulated. Some students of the disease contend that the spleen removes excessive numbers of platelets from the circulation, Troland and Lee (1938), and others have reported that a substance extracted from the spleens of patients with thrombocytopenic purpura and injected into rabbits causes a reduction of circulating platelets in these animals—but several independent workers have failed to confirm the findings (the paper of Rose and Boyer, 1941, will lead the reader into this literature). Lamarzi and Schleicher (1940) have championed the view that the disease is due to the production by the spleen of a factor which causes faulty maturation of the megakaryocytes in the bone marrow, Wiseman *et al* (1940), however, did not find evidences of such an effect in their marrow studies. Madison and Squier consider that some cases of purpura rest upon an allergic basis.

Simple Nonthrombocytopenic Purpura—In these cases the chief fault seems to be chargeable to an idiopathic alteration in the permeability of the small vessels, since often there is no abnormality in the blood at all or merely a prolongation of the bleeding time, occasionally, however, both failure of clot retraction and prolongation of the bleeding time are seen, but by definition marked reduction in the platelet count cannot occur in this group. The purpuric lesions appear in crops which recur at intervals of weeks to years, often without any other symptoms, though many patients complain of joint pains especially in the knees, with advancing age this type of purpura tends to die out altogether. Davis (1939) has described an hereditary familial form of this disease.

Secondary Purpuras—Purpuric manifestations are observed not infrequently during the course of other disturbances, of which the following is a partial list: infectious diseases, such as hemolytic streptococcus septicemia, meningococcemia, bacterial endocarditis, miliary and generalized tuberculosis, scarlet fever, typhoid fever, etc., focal infections especially in children, scurvy, endocrine disorders (the triad of sepsis, purpura and bilateral adrenal hemorrhage, seen almost exclusively in children, is called Waterhouse-Friderichsen syndrome), aplastic anemia, acute leukemia, excessive irradiation, senility, cachectic states, especially if due to malignant disease, chronic liver and kidney disease. It is thought that these purpuras are not of the thrombopenic sort as a rule, save in those instances when direct disturbance of bone-marrow function has occurred, but as a matter of fact the group has not been exhaustively studied. The purpuric signs disappear with recovery from the primary disease or intoxication.

Schönlein-Henoch's Disease—In this type of purpura the attack begins with malaise, fever, sore throat, and polyarticular pains, all of which usually precede by some time the eruption which often partakes of the nature of purpura, urticaria, and erythema in combination. Or there may be abdominal or renal crises due to the extravasation of blood into the intestines or kidneys. In some instances purpuric lesions fail to appear in the skin, which makes the diagnosis by no means easy. All the manifestations of this disease seem

to be ascribable to alterations in capillary permeability, which are believed to rest upon an allergic basis

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Unquestionably the most important single factor in treatment is to make every effort to determine the type of purpura with which one is dealing, since a major surgical procedure which may be necessary and life saving in one type would be contraindicated and absolutely inexcusable in another. Likewise the failure to recognize an underlying drug intoxication, or a subclinical ascorbic acid deficiency, or a neoplastic malady or leukemic blood dyscrasia, might have the direst results. The subject is confusing admittedly, but accurate diagnosis is mandatory notwithstanding.

Thrombocytopenic Purpura —The Allergic Approach—A sufficient number of case reports has now accumulated to warrant the careful study of every patient from the standpoint of drug sensitization, instances in which attacks have been definitely ascribable to the following drugs have come to my attention: arsphenamines, gold salts, sedormid, nrianol, phenobarbital, quinme, ergot, sulfonamides. Foods to which the patient responds allergically have also been indicted. Squier and Madison (1937), by limiting treatment to such dietary manipulation as eliminated foods suspected on the basis of history and skin tests have been able to effect striking clinical improvement and gradual marked rise in platelet level in their 3 patients. Dutton (1938) reported similar success in the single case which he treated in this manner. Several observers have rather airily dismissed this sort of approach simply by saying that in their experience the allergic constitution did not seem to be involved in the mechanism of purpura, but I have seen no evidence in their reports that the painstaking and expert sort of allergic study required here had been made in their cases. Splenectomy is a radical procedure, transfusion is only a palliative measure, if there is a chance that meticulous allergic study might solve the puzzle in many of these cases it seems unfortunate that more of them are not submitted to such study.

Splenectomy—It certainly seems to have become the consensus in the profession that splenectomy is the treatment of choice in severe cases. Kraeke (1941) not himself a surgeon, says 'I have never seen a severe case of this disease that finally did not require splenectomy.' It seems to me that treatment with medical measures is merely temporizing until the inevitable time comes for removal of the spleen. Sometimes the staunching of the hemorrhage occurs before the patient has been removed from the table or even before the abdominal incision has been closed. According to Elliott (1939), of the Spleen Clinic of the Presbyterian Hospital in New York, the results are highly satisfactory in about 85 per cent of cases, Robertson (1938) suggests that some of the failures may be due to the presence of accessory spleens elsewhere in the body, Pernokis (1942) felt certain that one of his patients died as a result of hyperplasia of an accessory spleen noted during the operation but not removed. Of the several follow up studies available the one which extended over the longest period seems to be that of Vaughan and Wright (1939), whose 6 patients were free from bleeding phenomena, and 4 were known to show normal platelet levels, at periods of from ten to fifteen and one-half years after operation. But not even the warmest advocates of this measure rush their patients at once into the operating room. Witness Giffin, who from

the standpoint of a physician and not a surgeon reviewed the Mayo Clinic experience in 1936 in not one of the cases in this series was it felt necessary to operate within ten days of the onset—days in which other measures, especially transfusion, were being given full trial. In the Johns Hopkins Hospital series, reported by Wintrobe *et al* in 1937, splenectomy was performed in only 10 of 62 cases.

The reason for the apparently undeniably remarkable effect of splenectomy in many cases is not at hand, for usually the platelet count does not reach normal until many days after hemorrhage has ceased. Sometimes postoperatively the platelet count goes down again to the earlier level and yet the patient remains free of symptoms. Askey and Toland (1933) stated that many patients show clinical improvement after removal of the spleen without the blood reflecting this change in a single particular. However, Nygaard (1940), of the Mayo Clinic, says that study of any large group of cases show that the least satisfactory results are found where more or less marked reduction of circulating platelets follows operation. It is also true that patients sometimes have recurrence of symptoms though the platelet count has mounted to and remained above normal postoperatively (Brown and Elliott, 1936). Whether or not operative trauma alone may suffice to explain the good results is a question which cannot be lightly smothered. Giffia (1930) admits inability to refute the assumption categorically but feels that the limited data at present available strongly indicate the useful office of removal of the spleen itself. An observation not to be lightly overlooked, however, is that of Steiner and Gunn (1931), namely, that operations in rabbits involving an amount of trauma comparable to that during removal of the spleen induce a platelet rise differing neither in time of occurrence, degree nor duration from that following splenectomy.

Transfusion—The object of transfusion in purpura is not solely to supply blood lost through hemorrhage, since the anemia usually rapidly disappears through the body's own spontaneous efforts once bleeding ceases but also to introduce platelets in the hope of stopping hemorrhage, bleeding usually begins when the normal platelet count of 250 000 to 400 000 has fallen to 50 000 to 75 000, but not invariably. In an earlier day, Larrabee, among others, arguing that a single transfusion seldom increases the patient's platelet count more than 20 000, advocated large transfusions of as much blood as the donor could safely give, the patients being mostly young persons with normal hearts, he felt there was little danger from overtransfusion. Many observers of that period also believed that citrated blood was inferior to whole blood. Nowadays, however, both positions are reversed. Jones and Tocantins (1933), and Patek (1936), express the consensus in advocating frequent—daily in some instances—transfusions of 100 to 300 cc of citrated blood. Wiseman *et al* (1940), however, are again advocating transfusions of full size (500 cc for adults) and see no difference in effectiveness between citrate and whole blood. Potts' (1932) results with 8 to 10 cc of whole blood given intramuscularly probably are based upon some mechanism other than the supplying of the platelets. Wiseman *et al* declare categorically that these injections are of no value, but in the interesting native African disease known as "oolalai," which Blackie (1937) considers thrombocytopenic purpura, such injections are found to be highly effective.

Miscellaneous Agents—Many remedies have risen and fallen through the

years, the following may be currently mentioned (a) Congo red in 4 cases resisting other treatment Brühl (1933) reported prompt arrest of bleeding by intravenous injection of 10 to 20 cc of this dye in 1 per cent aqueous solution Taliaferro and Haag (1937) showed that such dosage causes a decrease in coagulation time in normal individuals, but Richardson (1939) was unable to confirm this finding, the rationale of Congo red employment seems very doubtful (b) Ascorbic acid (cevitamic acid, vitamin C) Junghans (1935), Vogt (1935), and Miller and Rhoads (1936), have reported successes with this agent But Davidson (1937), employing the recommended dosage of 100 to 300 mg intravenously daily for seven to ten days, did not favorably influence either the platelet level or the symptoms in his 3 patients, Stephens and Hawley (1936), and Wright and Lihensfeld (1936), are also doubtful of the value of this vitamin approach (c) Hypercalcemia Lowenburg and Ginsburg (1936) incidentally noted cessation of bleeding in a patient in whom hypercalcemia had been induced Recalling the experience later, they deliberately employed the method in a second patient whose purpuric symptoms did not yield to other measures, subcutaneous injection of 3 cc (60 units) of parathyroid extract and intramuscular injection of 10 cc of calcium gluconate solution was made daily for three days, the patient being a child of seven years Serum calcium and phosphorus rose very high but reverted to normal promptly after cessation of treatment Toxic manifestations during the hypercalcemia were vomiting, weakness, anapathy and lethargy With the establishment of hypercalcemia definite symptomatic and hematologic improvement set in, subsequent examinations after discharge from hospital revealed the patient to have remained in a practically normal state Ainsworth *et al* (1937) succeeded with this treatment in their 2 cases, and Levine and Michelson (1940) in their single case Mathewson and Cameron (1937) failed in their case, and both Rosenthal (1939) and Wiseman *et al* (1940) report unfavorably, but they give no details of their cases (d) Irradiation this measure has had plenty of time to establish its worth but still has not done so in a way that is convincing to most observers (e) Snake venom the Council on Pharmacy and Chemistry reviewed the record of this agent in 1940 and did not find it acceptable (f) Sesame oil Olson (1939), in 2 cases, failed to confirm the earlier report that this so-called "T factor" is of value (g) Citrin (vitamin P) the evidence that this agent is of value in thrombocytopenic purpura *per se* is not yet convincing

Simple Nonthrombocytopenic Purpura—It is obvious that there is no warrant for the use of drastic measures in these cases That the allergic approach is most promising is indicated in the studies of Eyermann (1935) and Diamond (1936)

Secondary Purpura—The treatment is that of the underlying major disturbance

Schonlein-Henoch's Disease—The fact is well established that these attacks are practically always of an allergic nature, treatment therefore consists principally in the search for the guilty allergen and the attempt to eliminate it from the diet or environment or to desensitize the patient to it. Of course splenectomy and all other drastic measures are contraindicated, cases are on record, however, in which laparotomy has revealed intussusception and true hemorrhagic appendix Possibly one should note Jersild's (1933) single case in which all the symptoms disappeared under vitamin P

(citrin) therapy and returned when this therapy was stopped, beginning administration was 50 mg daily intravenously, later dosage was 20 mg twice weekly intramuscularly

HEMOPHILIA

Hemophilia is an hereditary hemorrhagic disease of unknown etiology, which is transmitted by the female but occurs only in the male. Macklin's (1928) studies showed that (a) a man afflicted with hemophilia will have no hemophilic children provided he marries a woman who is not a carrier, (b) the sons of such a man will be normal and unable to transmit the defect, (c) his daughters will all be carriers, though outwardly normal liable to give the active disease to half of their sons, (d) half the daughters of a woman who is a carrier are apt to be carriers themselves transmitting the defect, as their mother did, to half their sons as the active disease and to half their daughters who will be carriers in their turn, half the daughters and half the sons of a woman who is a carrier are apt to be normal, (e) since, in a hemophilic family it is impossible to tell which women are carriers until they reproduce, it is advisable for all women in such a family to refrain from having children, (f) the only persons in a hemophilic family who can marry with impunity are the unaffected males and their descendants. Macklin's (1939) later study indicates that there is no adequate basis for the idea that the sex ratio is disturbed in hemophilic families in favor of perpetuating the malady. There are obscure types of the disease which in the matter of heredity are not easily fitted into the classical framework, but these pages are of course not the place for an analysis of such rarities.

The characteristic abnormality in the blood of individuals with classical hemophilia is prolongation of the coagulation time, an alteration, however, which varies apparently from day to day and perhaps even from hour to hour therefore at some periods the patients are much more likely to bleed than at others. Bleeding time, clot retraction (once clotting begins), and the platelet count are normal, the Rumpel Leede test for capillary erythrocyte permeability is negative. Quick *et al* (1935) find prothrombin quantitatively normal while Brinkhous and his associates (1939) report an abnormally slow conversion of this prothrombin into thrombin such as would result if thromboplastin were sluggishly liberated from the platelets. For a number of years indeed, the possibility of a qualitative alteration in platelets has been engaging the minds of investigators. It seems almost certain that neither calcium nor fibrinogen disturbances are present. In the years since 1936, Patek, Pohle and their associates in this country, and Bendien and Van Creveld in Holland, have been presenting strong evidence in support of the view that blood plasma contains a specific substance which accelerates the process of clotting and that this substance is deficient in hemophilic blood, if I understand Howell's (1939) current viewpoint it is that this postulated 'globulin substance' is practically identical with plasma thromboplastin, which he like others finds much reduced in amount in hemophiliacs.

The disease usually makes itself apparent at an early age. External

anyone to have formulated a definite opinion since the substance is difficult to prepare and is not yet generally available. Lozner and Taylor (1939), of this same group of investigators, have now prepared a euglobulin substance which is thought to have some advantages over the first preparation—so the investigation is seen to be continuing and one may hope that something of a generally applicable nature will result. Eley *et al* (1936) have prepared an anticoagulant substance (presumably a tissue thromboplastin) from human placenta, which has the advantage of being suitable for administration by mouth, but this too is still in the experimental stages. The substance which Timperley *et al* (1936) obtained from egg white has apparently come to little, at least I have seen no recent reference to its employment. Protein sensitization has been tried off and on for years but there is no convincing evidence of its value. The estrogenic substances, toward which we looked for a time so hopefully, are now recognized also as failures. Recently there has been a flurry of interest in oxalic acid and the proprietary preparation, koagamin, which resulted from these studies, but Johnson (1941), at the University of Rochester, has used both oxalic acid and the proprietary preparation without effect in 5 cases of hemophilia.

In the control of accessible hemorrhage none of the older hemostatics has shown any consistent worth, perhaps the one with the most honorable record is tannic acid, used as a dusting powder. There are favorable reports on the use of snake venom in small series of cases. In England Macfarlane and Barnett (1934), and Baker and Gibson (1936) employed Russell viper venom in a dilution of 1 : 10,000, in the United States, Rosenfeld and Lenke (1935) used 1 : 5000 tiger snake venom. McGavack (1940) did not succeed with venom solutions but used viper venom in powder form successfully in one case of bleeding following tooth extraction, he has also successfully employed the powdered globulin substance of Pohle and Taylor, previously mentioned. Solé (1935) reports that he has had good results from applying iodoform tampons saturated with human milk, anything is worth trying perhaps. Where stitching is necessary, catgut sutures which will not have to be removed later, elevation of the part if possible, and absolute rest, are about the only things to resort to. According to Birch (1933) hemorrhages from the loosening or loss of deciduous teeth are best treated by making a mold of soft wood, cork or gutta percha which fits over the gum and fastens tightly to the teeth on either side of the bleeding point, she lines the mold with a thin layer of cotton soaked in ovarian extract (others use powdered snake venom), and keeps the patient on a liquid diet. Extraction of a tooth should take place only if absolutely unavoidable, before the tooth is removed a mold such as the above should have been prepared to hold cotton in place in the cavity. In 2 instances of bleeding tooth sockets Warner *et al* (1939) have promptly controlled hemorrhage by spraying on their purified thrombin preparation.

Of course hemorrhage into a large joint calls for rest of the joint, with mechanical immobilization if necessary, until pain disappears and the blood is largely absorbed, salicylates are helpful. When there is intense pain the question arises as to the possibility of aspiration. Key (1932) says that it has been carried out a number of times without ill effects, but probably in all of these instances the patient was, as in his own case, in a nonbleeding phase. Certainly fatal hemorrhage and infection has resulted from such aspirations. Orthopedists are rather impatiently awaiting the discovery of a medica-

cure for hemophilia so that they may begin the correction of the deformities, but I doubt that many of them are daring to undertake open operations at the present time.

HEMORRHAGIC DISEASE OF THE NEWBORN

(See *Vitamin K Deficiency*)

HYPOPROTHROMBINEMIA

(See *Vitamin K Deficiency*)

HEMORRHAGE IN OBSTRUCTIVE JAUNDICE

(See *Vitamin K Deficiency*)

CIRCULATORY DISTURBANCES

CIRCULATORY DISTURBANCES

FUNCTIONAL DISTURBANCES OF THE HEART

Occasionally a functional heart disturbance in an individual of fairly robust mental and physical status will follow upon the shock of a sudden cardiac death in a near associate, but cardiac neuroses are usually seen in persons of definitely neurotic type and often with a history suggestive of neurotic ancestry. There is complaint of transitory palpitation, rushing of blood in various parts of the body, throbbing, and many other symptoms which are described with the particularity so habitual to the neurotic. When there is pain it is usually felt over the left chest where the heart is supposed to be rather than under the sternum. In the condition known as neurocirculatory asthenia (effort syndrome, soldier's heart, irritable heart), the symptoms—giddiness, faintness, palpitation, precordial pain and breathlessness—are the symptoms of effort and mark the patient as one who is physically inadequate to the ordinary stresses and strains of an active life.

THERAPY

These patients comprise a very considerable portion of the 'heart' cases seen in an average general practice, and the fact that the elements of their treatment can be set down in a relatively few lines of print by no means justifies a contemptuous attitude toward the group. The more robust will be cured by complete examination and the reassuring statements of a doctor in whom they have confidence, but what is needed by the majority of the patients is just exactly the hardest thing in the world to supply, namely, an entire readjustment to life. If there is some one thing which is causing the basic unhappiness upon which the cardiac neurosis is engrafted, the bringing of that thing out into the open and the attempt to reconstruct a life in which that particular fact is accorded no more than its proper share of importance, will oftentimes greatly relieve the patient, though if he is basically neurotic the relief will usually be only temporary. In no case must a cardiac neurotic be permitted to continue in the belief that he has the least thing the matter *with his circulatory apparatus* but there are ways and ways of assuring him of this fact. Perhaps the best method is to demonstrate his freedom from symptoms while enjoying some diversion in which he is for a time freed from his inordinate load of cares, to ridicule or to scold is almost certainly to toss him to the quacks.

The avoidance of physical and mental fatigue is important and can usually be accomplished in some degree if the patient is at all tractable.

In neurocirculatory asthenia definite attempt to build up the patient's tolerance for that amount of physical exertion which is necessary in his occupation should be made, but it is seldom possible to bring him up to the normal of physical endurance. Carefully graded exercise, with special stress upon the necessity of obtaining not only a long night's sleep but a midday rest as well, is desirable. White (1942) points out that it has been found wise in England to treat the average run of the cases of neurocirculatory

asthenia that have arisen in the armed forces during the current war as ordinary medical cases of fatigue without referring them to either cardiologist or psychiatrist, in this way avoiding overemphasis of either heart or mental state in the patient's mind

PERICARDITIS

Acute pericarditis rarely occurs except as a complication of one of the infectious diseases, particularly tonsillitis, sinusitis, tuberculosis, scarlet fever, acute rheumatic fever, pneumonia, and sepsis (septicemia), though it occasionally occurs as a postoperative complication and as a terminal condition. It is sometimes recognized in chronic nephritis. In fibrinous pericarditis without effusion the symptoms are those of the primary disease plus pain in the precordium, or referred to other parts of the body, and a characteristic friction rub heard upon auscultation. When effusion occurs the patient usually becomes anxious, more or less cyanotic and dyspneic, and often very restless. Pressure on nerves and other structures may cause cough, aphonia, difficulty in swallowing, hiccup, vomiting, etc. The pulse rate usually rises very high and becomes irregular. The area of dullness at the base of the heart is increased and there may be actual bulging of the precordium, the apex impulse usually disappears. As the fluid increases the friction rub diminishes and, with a large effusion, the heart sounds are no longer audible. Despite the glibness with which it is usually described, pericardial effusion is by no means always easy to diagnose. The prognosis in fibrinous pericarditis is always good, in the effusion cases, if the fluid is tuberculous or becomes purulent (suppurative pericarditis), death is the usual outcome, but in rheumatic cases the fluid is usually absorbed. Acute pericarditis was probably first discovered by Avenzoar, of Córdoba, in the twelfth century.

There is also a chronic type of constrictive pericarditis known as "Pick's disease." Its chief characteristics seem to be (a) insidious onset of dropsy in a young person without nephritis or a markedly abnormal heart, (b) enlarged liver, ascites and prominence of jugular veins, (c) low systolic arterial pressure and a small pulse pressure and paradoxical pulse. History of antecedent pericarditis or polyserositis is a helpful clue. The patients are condemned to semi-invalidism unless properly treated.

where remarkably quick subsidence of the effusion sometimes takes place. When the fluid becomes purulent, the attempt to establish surgical drainage must be made at once. Bigger (1939) and others stress the necessity of making every effort to arrive at an early diagnosis since surgical procedures alone offer whatever chance there may be of cure.

In Pick's disease the outlook has been completely changed through the introduction of surgical techniques facilitating removal of a portion of the thickened pericardium, relief of symptoms and "cure" often result.

ENDOCARDITIS

There are four main types of endocarditis. The *rheumatic* type develops during the course of an attack of rheumatic fever and is usually heralded by an increase in severity of this disease, i. e., more discomfort and a rise in fever. Precordial pain, increase in pulse rate, murmur, and often a considerable dilatation of the heart appear later. *Acute bacterial* endocarditis is also usually a secondary affair complicating one of the acute infectious diseases. Its diagnosis is usually based upon the appearance or increase in the signs of sepsis (septicemia) and the finding of a positive blood culture, though cardiac symptoms are sometimes prominent also. Some of these cases are so rapidly fatal as to have earned the appellation "malignant endocarditis." Then there are the cases of *subacute bacterial* endocarditis in which the patient with a pre-existing valvular lesion experiences a reinfection of the endocardium from an infectious process in the teeth, tonsils, middle ear, or other focus. Okell and Elliott (1935) have shown how very frequently the nonhemolytic streptococcus of the *viridans* type, the organism most often involved in these cases, enters the blood stream from septic mouths. Middleton and Burke (1939) stress the point that rheumatic valvulitis and congenital cardiac lesions are the most common precursors of this form of endocarditis. The disease runs an obscure febrile course until a murmur of growing intensity is detected, or petechiae on the extremities and visible mucous membranes and signs of splenic or kidney infarction make their appearance. Christian (1941) says that if malaise and fever, joint or muscle pains, nausea or loss of appetite appear in an individual, usually a youth or young adult known or found to have chronic valvular or congenital disease of the heart, and persist for more than one week without the development of evidence of other definite disease, the probability of subacute bacterial endocarditis is great. Positive blood cultures are easy to obtain and assist in making an early diagnosis. Death is usually caused by cerebral embolism. And finally there is the type of *nonbacterial* endocarditis, which is apparently comprised in the "atypical verrucous endocarditis" of Libman and Sacks, and the "thrombotic endocarditis" which Gross and Friedberg (1939) are studying.

I believe that Matthew Baillie (1761-1823) was the first to describe endocarditis.

THERAPY

In all forms of endocarditis the patient must be kept absolutely quiet, to which end the use of the ice bag, or in the asthenic individual hot applications,

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THERAPY

The treatment of acute pericarditis is the treatment of the primary disease. An ice bag placed upon the precordium in the robust, or hot applications in the puny, asthenic individual, are usually successful analgesic measures. Codeine, 1 grain (0.065 Gm.), morphine, $\frac{1}{4}$ grain (0.015 Gm.), or dilaudid, $\frac{1}{8}$ grain (0.002 Gm.), should not be withheld if pain is sapping the patient's strength, though it is well to restrict the opiates as much as possible because of their effect in locking the bowel. Salines, or enemas, are definitely indicated to prevent abdominal distention or straining at stool, both of which increase the load upon the heart. Aspiration of fluid brings such great relief in the effusion cases that it is held to be advisable to employ the procedure early and frequently, except perhaps in the rheumatic cases.

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THERAPY

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over the precordium is indicated, opiates should be used if pain and restlessness are severe. In the rheumatic type of the disease salicylates have no effect upon the endocardial process. Acute bacterial (malignant) endocarditis is best treated as a case of sepsis, the symptoms of which, indeed, usually dominate the picture, fever therapy seems to be of adjuvant importance in the gonococcal cases. With regard to subacute bacterial endocarditis the outlook is still very bad, but some new treatments are being tried nowadays. Lichtman and Bierman (1941) report the following results collected from the literature and their own experience at Mount Sinai Hospital in New York: (a) of 200 patients treated with the sulfonamides, 94 per cent died, (b) of 43 treated with sulfonamides and heparin, 88.5 per cent died, (c) of 45 treated with sulfonamides and fever therapy, 75 to 84 per cent died, the larger number of recoveries occurring if typhoid vaccine was used instead of physical hyperthermia. It is to be noted that the small and differing numbers of cases in these series make it impossible to draw any statistical conclusions from them. For methods of fever therapy, see the Index, and for sulfonamide methods see Sepsis and Pneumonia. Heparin, used in the attempt to prevent further thrombotic deposition on the surface of the vegetations, is usually employed according to the method of Kelson and White (1939): the contents of a 10 cc vial of heparin (10,000 units) are added to 500 cc of physiologic saline solution and given by continuous intravenous drip at such rate (usually 15 to 25 drops per minute) that the venous clotting time, which is normally below twenty minutes, is held at about one hour. The recent report of Leach *et al* (1941), representing the pooled experience of several clinics in Boston, indicated that possibly both sulfapyridine and sulfathiazole may have some value in subacute bacterial endocarditis—slight value to be sure, but still greater than any other agent has ever shown. Leach *et al* felt that heparin may also have been helpful in conjunction with the sulfonamides. However, 8 of the 22 heparin treated patients of Waitzkin *et al* (1942) died of cerebral hemorrhage during the administration of the heparin, so these observers quite naturally question the advisability of the agent's further employment, obviously the method is to say the least, still in the experimental stage. Polowe (1939) reports that splenectomy, introduced by Riesman, has been used in 4 cases: proved by blood culture, 1 of the patients recovered, in 12 unproved cases it was the impression of most of the attending physicians that the patients had benefited from the procedure, and 2 seem to have recovered.

ACUTE MYOCARDITIS

Acute myocarditis is always secondary to one of the acute infectious diseases—*always*, that is, unless one accepts as a distinct entity the rare "acute isolated myocarditis" described by Hansmann and Schenken (1938)—being particularly prone to occur during or after an attack of rheumatic fever, influenza, scarlet fever, typhoid fever, diphtheria (especially if antitoxin is too long delayed or given in too small doses), or sepsis. There is usually a decrease in blood pressure with an increase in heart rate and the appearance of some sort of irregularity, though it must be admitted that the

diagnosis of myocarditis is notoriously difficult to make, in diphtheria, brady cardia occasionally occurs and is almost invariably fatal. When acute heart failure makes its appearance the symptoms are the same as those of heart failure from any other cause.

THERAPY

The factor of greatest importance in the treatment of acute myocarditis is absolute rest. Not only should rest be enforced in all known cases, but in suspected cases as well, i.e., in all attacks of rheumatic fever and the other acute infectious diseases listed above, the patient should not only be kept in bed but must lie quietly in the bed. In rheumatic cases in children, Taussig (1935) advocates the use of considerable doses of sedatives—phenobarbital (luminal), $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.) three times daily, or codeine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015–0.03 Gm.) twice or thrice daily or even every four hours if necessary.

During the course of acute myocarditis in rheumatic cases drugs other than the salicylates, etc., are usually of little value. Most physicians look upon digitalis as a dangerous drug here because of its tendency to accelerate an already established heart block. The drugs which ordinarily whip up heart action—caffeine, metrazol, coramine, epinephrine (adrenalin)—are often recommended and probably freely used, but it seems to me that in the very nature of things they are contraindicated. We have no effective medication in the heart failure of acute myocarditis and had as well admit it. In some instances the degree of anoxemia will indicate resort to oxygen or the inability to take sufficient fluids and food by mouth will make it advisable to give dextrose in Locke's solution intravenously. In other instances venesection may relieve the right side of the heart of its load in time to be life saving. Or sponging to quiet the patient may be absolutely the therapy of choice. In short, meet the indications as well as they can be met with woefully ineffective nonspecific measures.

Following the subsidence of active symptoms the patient is not to be allowed to rise suddenly from bed and resume the ordinary rounds of play or duty. Strength testing by daily increases in pillow propping is mandatory, and even after the patient is got gradually out of bed, the return to full activity, if this will ever be permissible again at all, must be accomplished with extreme slowness. The schedule below, which guides Taussig in the management of children convalescing from acute rheumatic myocarditis, will indicate what is meant.

1st month	1st two weeks	Up in a chair two hours in P.M.
	2nd two weeks	Up in a chair two hours in P.M. Walking to bathroom
2nd month	1st two weeks	Up in a chair two hours in A.M. and P.M. Walking to bathroom
	2nd two weeks	Up 10 A.M. to 1 P.M. and 3 to 5 P.M. This generally includes being up at the table for the noon meal.
3rd month	1st two weeks	Up 10 A.M. to 1 P.M. and 3 to 6 P.M.
	2nd two weeks	Up 10 A.M. Out-of-doors 11 A.M. to 12 noon. Lunch 12:30 P.M. Bed 1 to 3 P.M. Up 3 to 6 P.M.
4th month	1st two weeks	Up 10 A.M. Out-of-doors one to two hours A.M. and P.M. Two hours rest in P.M. Bed 6 P.M.
	2nd two weeks	Up 9 A.M. Two hours P.M. rest. Bed 6 P.M.
5th month	1st two weeks	Up 7:45 A.M. Two hours P.M. rest. Bed 6 P.M.
	2nd two weeks	Up 7:45 A.M. School in A.M. ($\frac{1}{2}$ day) Two hours P.M. rest. Bed 7 P.M.

CHRONIC MYOCARDITIS

(See *Chronic Nonvalvular Heart Disease*)

ARRHYTHMIAS NOT OF PRIMARY THERAPEUTIC INTEREST

There are properly three groups of cardiac irregularities: first, those which might be called "normal" without too great impropriety, second, those which are entirely secondary to some other underlying pathologic process, and third those which must be combated upon the basis of their own independent existence. Obviously, in a book such as this, mere listing of the entities in the first two groups must suffice so that detailed attention may be given to the last, or therapeutically important, group. In *sinus arrhythmia* the heart rate gradually accelerates and retards usually synchronously with the phases of respiration, this occurs in all infants, many children and some adults, and disappears temporarily whenever the heart rate is increased in normal tachycardia, it appears occasionally during digitalis therapy and frequently as recovery from normal tachycardia takes place. *Sinus or normal tachycardia* is the acceleration in regular rate which occurs in hyperthyroidism, fever, exercise, shock, anemia, etc., the treatment is that of the underlying condition. The rare *paroxysmal ventricular tachycardia*, unlike the auricular form of tachycardia, is practically always a mere intercurrent affair in grave organic heart disease, it does respond very well, however, to quinidine therapy. In *normal bradycardia* the impulse is transmitted regularly but excessively slowly, this slow, regular rate is apparently normal for some individuals, but it also occurs in others during jaundice and in some of the deficiency states and at times during recovery from fever, and it must always be differentiated from true heart block. *Sinus pause* is the term used to indicate the occasional complete skipping of an entire beat which occurs now and then in healthy individuals—according to Levina (1936), under such diverse stresses as prolonged standing, a hot room, sudden twisting of the neck, the prick of a needle, the sight of blood, etc. The *heart blocks* which occur frequently in coronary and hypertensive disease, often during the course of diphtheria and rheumatic fever, occasionally in syphilitic cardiovascular disease, and very frequently during digitalis therapy, are *sino-auricular block*, in which an impulse failing to leave the node of origin provides a pause between beats of twice the usual duration, *first degree block*, an increase in conduction time between auricles and ventricles, usually detectable only with the electrocardiograph, *second degree or partial block*, in which, due to failure of some of the impulses to reach the ventricles, the auricles and ventricles beat in a rhythm of 2 to 1, 3 to 1, and so on, and *bundle branch block*, an electrocardiographically demonstrable delay or block of an impulse in one of the branches of the bundle of His. *Ventricular fibrillation*, for which there is no effective treatment, is practically always only a terminal event. *Pulsus alternans* is not a true arrhythmia but an alternation in force of the regular beats, the treatment is that of the underlying heart disease.

AURICULAR FIBRILLATION AND FLUTTER IN OTHERWISE NORMAL HEARTS

Auricular fibrillation is probably due to a self-perpetuating ring of excitation—"circus movement"—about the mouth of the superior vena cava, the auricles being maintained in rapid fibrillary contractions, to only a small number of which the ventricles respond. The pulse is extremely irregular in rate and unequal in force, and the count at the wrist, though usually high, is often less than at the apex due to the failure of some of the weak ventricular contractions to open the valves or initiate the wave; in rare instances the "pulse deficit" may be so great as to produce a rate at the wrist lower than normal. In auricular flutter the circus movement is slower than in fibrillation and it is responded to by the ventricles at a regular rate and in a definite ratio; i.e., the relationship of ventricular-auricular impulses will be 1 to 2 or 3 or 4. Flutter is detectable only through study of the electrocardiogram.

Both of these arrhythmias, but especially fibrillation, have long been known frequently to complicate congestive heart failure from the usual causes, and likewise to appear not infrequently in advanced thyrotoxicosis. In recent years it has also been recognized that they may occur in a heart otherwise apparently entirely normal. In these instances palpitation is the most common symptom, pain the rarest; sometimes there is breathlessness, pallor, vertigo and nausea. Usually the paroxysms do not last longer than a week, but rarely an attack has persisted as long as a year and then terminated spontaneously. During the attack of fibrillation exercise increases both the rate and irregularity of the contractions. In Brill's (1937) case severe congestive failure appeared but entirely cleared up upon cessation of the arrhythmia. Most of the patients are at or past middle age when their first attack is experienced; frequency of paroxysms is variable but tends to diminish with the passage of time; the studies of Orgain, *et al.* (1936), and Willis and Dry (1941), indicate that the prognosis for life and for the maintenance of cardiac function is usually excellent.

THERAPY

The treatment of these arrhythmias when they complicate congestive failure from other causes is usually quite secondary to treatment of the failure itself; i.e., when all that is possible has been accomplished by the use of digitalis, the advisability of using quinidine must be separately weighed in each case—the matter is discussed in detail under Congestive Heart Failure. At present we are concerned only with fibrillation or flutter in otherwise normal hearts; i.e., in postoperative cases of thyrotoxicosis in which spontaneous return to normal rhythm has not occurred, and in individuals who experience such paroxysms as above described. In a fibrillation of this sort digitalis is not regularly of value and quinidine is the drug of choice. It was a patient with paroxysmal fibrillation who first brought to Wenckebach's attention, in 1912, the use of quinine in the malady; Frey's investigations later caused the substitution of quinidine sulfate for the older drug. Quinidine is rather consistently effective, and increasing experience has shown that serious reactions are of infrequent occurrence in patients whose hearts are normal except for the arrhythmia. However, there is not always need to use the drug in these cases, since most of the paroxysmal

attacks suddenly terminate spontaneously in a few days. The following symptoms of quinine intoxication are those most usually seen (Kohn and Levine [1935]) nausea, vomiting, epigastric distress, diarrhea, headache, palpitation, tinnitus, apprehension, mental depression, flushing, sweating, syncope, disturbances of vision and extreme excitement are of much rarer occurrence. Papular, petechial and scarlatinous rashes, and urticaria and inflammatory edema of the face have been reported. The more serious reactions, rare and usually occurring only in individuals with grave organic heart disease, are (a) sudden ventricular fibrillation and heart failure, (b) sudden death with respiratory failure, a type of effect reproducible in laboratory animals, (c) embolism—it is interesting to note that after a period in which we were somewhat in doubt as to the increased incidence of this phenomenon under quinidine's influence, Kohn and Levine's (1935) reexamination of the evidence reaffirmed earlier statements that the drug does tend to cause this accident to occur through suddenly restoring normal rhythm, more recently still however, Smith and Boland (1939) express themselves as very skeptical of this.

Perhaps the most usual method of employing the drug in such cardiac-normal individuals as we are considering here is that described by Brill (1937), who gives a test dose of 3 grains (0.2 Gm)—which alone was enough to arrest the paroxysm in one of his cases—and, if there are no untoward effects in six to twelve hours, begins administration of 5 to 6 grains (0.3–0.4 Gm) at four to six hour intervals until normal rhythm is restored or the appearance of toxic symptoms causes discontinuance. However, in using the drug following digitalis when auricular fibrillation has complicated preexisting heart disease, recent experience has shown that a more intensive type of therapy is often more effective. A dosage scheme of this type, as described by White and Glendy (1936), is after the test dose of 3 grains (0.2 Gm), give 6 grains (0.4 Gm) every two hours for 5 doses, if arrhythmia persists after these 30 grains (2 Gm) have been given, 1 or 2 more doses may be cautiously given, or the program may be repeated on the following day. Quinidine is rapidly excreted and cumulative effects need not be feared, but patients receiving these large doses should be in bed under close supervision and should if possible have an electrocardiogram made before the first, third and fifth doses. White and Glendy consider that severe symptoms of cinchonism, tachycardia of over 150, or intraventricular block evidenced in the electrocardiogram, demand omission of the drug.

Willius (1939) says that it has become customary at the Mayo Clinic to give 1/60 grain (0.001 Gm) of strychnine sulfate three times daily as supplementary medication if quinidine alone has not restored normal rhythm in three days.

For prevention of recurrence of auricular fibrillation, Brill uses 3 to 6 grains (0.2–0.4 Gm) once a day, but White and Glendy sometimes use such dosage as often as four times daily (even at three-hour intervals in some instances) for long periods of time, Gold (1940) also finds the larger dosage preferable, sometimes building up to as high as 40 or 50 grains daily. Messeloff (1939) feels that practically adult dosage may be safely administered to children; his series of 12 children so treated ranged in age from six to fourteen years.

In auricular flutter it is the consensus that full digitalization should be

preferred to the use of quinidine, the flutter is often converted into fibrillation which in turn ceases when digitalis administration is stopped. If digitalis fails then quinidine is to be tried.

PAROXYSMAL AURICULAR TACHYCARDIA

In this disturbance the patient becomes aware of a sudden great increase in the heart rate usually to from 120 to 180 beats per minute. The rhythm is regular and the rate is not decreased during rest. Such a paroxysm may persist for hours or even for many days, and the attacks may recur frequently for weeks, months or years. Individuals without demonstrable cardiac pathology are just as liable to these paroxysms as are the victims of heart disease, the young are more often affected than the old. Hubbard (1941) has reported 9 cases in infants under one year. The attacks terminate just as suddenly as they begin, and in most instances without having caused any disturbance other than distress and palpitation, in rare instances however, there are associated neurogenic symptoms such as polyuria, sweating, and dilatation of the vessels of the skin. Mild symptoms of transient congestion have been occasionally recorded. Some men are beginning to be interested in the possibility of an allergic origin of paroxysmal auricular tachycardia.

THERAPY

Mechanical Measures—Pressure on the carotid sinus to induce arresting vagal stimuli often dramatically stops such an attack, Gold (1940) says the measure succeeds in about half the instances. Firm pressure is made over the carotid artery below the angle of the jaw and sustained for ten to fifty seconds, pressure should not be made upon both sides at once. Firm pressure over the eyeball is also often effective but it is painful. There are individuals who can stop an attack by indirect stimulation of the inhibitory mechanism such as by deep breathing or holding the breath, vomiting, swallowing a hard bolus of food, or by assuming various postures.

Acetyl- β -Methylcholin (Mecholyl)—Starr (1936) introduced the use of this drug which causes effects analogous to vagal stimulation. The attack was quickly terminated in 88 per cent of 75 instances in 37 patients. In 20 per cent of the instances carotid pressure was effective during the period of the drug's action though it had failed before. Mecholyl is given subcutaneously in dosage varying, according to age and weight of the patient, from $\frac{1}{2}$ to 1 grain (10–60 mg). The injection is followed by a sudden sensation of warmth in the face, hyperpnea, sweating and salivation, and sometimes a sense of tightness across the chest. The patient should be prone when injected. In some instances of failure, repetition of the same or a larger dose after half an hour may bring success. Gold (1940) has given as much as 1 grain (60 mg) at one time intramuscularly, but the drug should never be given intravenously. Walsh and Sprague (1940) used 5 mg doses in a child of five years. One can add to the effect by vigorously massaging the site of injection. Nausea and vomiting are perhaps the first symptoms of overdosage. An

asthmatic attack seems to be precipitated in susceptible individuals and momentary heart block has also been noted in a few instances, coronary disease absolutely contraindicates the use of mechohyl Starr found that atropine sulfate, $\frac{1}{32}$ grain (0.0012 Gm) intravenously, terminates any of these reactions almost at once. It is felt that mechohyl is less effective when patients have been receiving quinine or digitalis, and that in any case it is drastic therapy not to be employed unless other measures have failed.

Quinidine—This drug is much used in combating the paroxysms, dosage, reactions, etc., are considered under Auricular Fibrillation, failures occur perhaps as often as successes. Levine (1937) succeeded in 2 cases with only 3 grains (0.2 Gm), but Gold (1940) says that large doses of the order of 10 grains (0.6 Gm) every two hours until 40 to 50 grains have been given may be necessary, he says and Eldahl (1940) had reported the same thing that $7\frac{1}{2}$ grains (0.5 Gm) of quinine dihydrochloride in 20 cc of fluid intravenously may be more effective (but see Malaria before nonchalantly injecting quinine). Gold feels that, next to digitalis, this is the best drug to use in attempting to prevent recurrences.

Emetics—Weiss and Sprague (1937) used the syrup of ipecac in 14 cases successfully in each instance, this is an indirect method of stimulating the vagus. Ideally, a dose of 1 to 2 drachms (4–16 cc) was given initially and repeated in the same or a larger dose if neither vomiting nor the desired effect was produced in forty five minutes. Practically, however, it seems to have been necessary to develop the dosage, number of doses and time intervals separately for each patient. Gold (1940) seems to have a high opinion of ipecac and says also that not infrequently $\frac{1}{8}$ grain (0.003 Gm) of apomorphine hydrochloride will accomplish the same thing.

Digitalis—Failure usually results from the use of this drug. However, a number of years ago Levine and Blotner presented 4 cases in which keeping the patient digitalized (beginning with full doses and finally employing maintenance doses of approximately 2 grains of leaves, 0.13 Gm, per day) was effective in preventing recurrence in individuals prone to have many attacks during a year. This is a small number of cases, but it is suggestive that the failure of most workers to get satisfactory results may be due to their small dosage of the drug. In his book, Levine (1937) reaffirms this position.

Gold (1940) also feels that digitization, with perhaps even double Levine's dosage is the most effective safeguard against recurrences. Hubbard (1941) used digitalis with satisfaction in most of his infants under one year digifoline intramuscularly in dosage of 0.05 to 0.1 Gm.

EXTRASYSTOLE

Premature systoles occur at some time in the life of most individuals, the phlegmatic often do not notice them at all, but in the nervous individual the abnormality is quite annoying. The heart usually 'thumps' or 'turns over' and then there is a long pause before the next beat occurs, this compensatory pause, due to the occurrence of an extrasystole during the period

of diastole, may be felt at the wrist and is usually equal in length to the time of two normal beats. These premature contractions, when they occur over a long period of time, may become a serious matter in that the patient often loses appetite and the ability to sleep and may even suffer a considerable impairment in general health, because of nervous worry. If associated with any demonstrable cardiac pathology, as is usually the case, extrasystole is quite without direct significance but since this phenomenon sometimes heralds the beginning of serious heart maladies it is always incumbent upon the practitioner to make a thorough examination of his patient before pronouncing the matter of no moment. Some men are thinking of the possibility of an allergic origin in some instances of extrasystole.

THERAPY

It is one thing to tell a patient that his heart is quite all right and another to get him to believe it in face of the heavings of which he is aware in his chest. Many individuals are quite capable of believing, during the busy daylight hours, that what the physician tells them is true but when night comes and they lie bedfellows with their misbehaving hearts apprehension grips them hard. It is wise not to overlook the advantage of reestablishing the habit of sleep by the use of sedatives or hypnotics for a while (see *Insomnia*).

Quinine, or Quinidine, and Strychnine—Many years ago Wenckebach the late authority on arrhythmias wrote "I have found strychnine in small doses helpful in cases of extrasystole in otherwise normal as well as in diseased hearts, but very often it did not act strongly enough, or it lost its action very soon. In these last cases I tried the combination of quinine and strychnine and found that this form of treatment had complete success in the great majority of my cases. I have given from 0.3 to 0.4 Gm (5 to 6 grains) of quinine daily, plus 2 or 3 mg ($\frac{1}{16}$ – $\frac{1}{8}$ grain) of strychnine through periods of ten days. My experience with this treatment since the year 1915 has been so favorable that I am convinced that whoever will try it will come to the same conclusion." The rationale of strychnine's use here is certainly difficult to understand, nevertheless, Carter and Traut (1935), using the more modern quinidine instead of quinine, have also reported better results when employing strychnine at the same time.

Quinidine—The methods of using this drug are detailed in *Auricular Fibrillation*. It is often effective.

Potassium Acetate—Sampson and Anderson (1932-1936) have found this salt, in 25 per cent solution by mouth effective in about half of the cases of extrasystole or tachycardia in which they have employed it, most of the failures, however, being in cases such as we are considering here (i.e., those having no apparent organic basis). The usual method is to attempt to prevent extrasystole during the night by administration of 45 grains (3 Gm) of the salt upon retiring, and repeating this or a larger dose after three hours if the first has been ineffective. Sampson looks upon advanced nephritis as a contraindication to the use of the drug. He has seen 4 paradoxical instances in which the administration of potassium either increased the extrasystole or actually produced paroxysmal ventricular tachycardia.

Aminophylline—It has been reported that coronary dilators will occasionally abolish this arrhythmia even in the absence of any cardiac abnormality.

mality These drugs have the advantage at least of being free from danger, see methods in Coronary Disease.

HEART BLOCK

(Adams Stokes Syndrome)

Complete heart block, with its associated symptoms, is a definite symptomatic entity, the block being due to arteriosclerotic, syphilitic, tuberculous, rheumatic, or adipose changes in the conduction tract, it should be noted however, that at autopsy some cases have been found to exhibit no lesions of the bundle. The victims of this disease usually have a pulse rate of between 25 and 40 and suffer fainting spells which often occur at such frequent intervals that the patient is in almost constant anguish. The syndrome usually makes its appearance in individuals past middle age, and in its milder grades is not incompatible with a normal duration of life, especially in those who are fortunate enough to live in partial retirement, but from one of the syncope attacks the patient finally does not recover.

This disease was described by Robert Adams, in 1826, and shortly thereafter by William Stokes—both leading members of the great Dublin school of the first half of the nineteenth century—but Flaxman's (1937) interesting historical study reveals that descriptions had in fact been published before this time.

THERAPY

Atropine—Atropine paralyzes the vagus endings and should therefore release the heart from vagal inhibition, but as a matter of fact we do not as yet definitely know to what extent the ventricles are under this control. It is known, however, that vagus tone as a whole in man is greatest under thirty years and markedly decreases after fifty—which fact in itself would be quite sufficient to explain the usual failure to quicken the heart in Adams Stokes disease most of whose victims are elderly. The drug is used in large doses, 1/20 to 1/12 grain (0.003–0.005 Gm.), subcutaneously.

Epinephrine—Epinephrine is used because of its well known ability to stimulate the sympathetic innervation of the heart and thus to cause an increase in rate. Dosage is 0.3 to 0.6 cc. of the usual 1:1000 solution, subcutaneously, never intravenously. Though admitting, in agreement with others, that epinephrine is by no means always successful in combating attacks, Gilchrist (1934), who has apparently closely studied this disease, states that no other drug has proved more effective, and he therefore feels that since we cannot as yet predetermine which patients will and which will not benefit, this drug should be given a trial in the treatment of all cases.

In dire emergency the drug may be injected intracardially. Eashy *et al.* (1935) briefly describe the method: "Select the fourth intercostal space, at the upper border of the fifth rib close to the sternum. Use iodine. Take a long, thin needle, 6 to 10 cm. in length. Insert as far as the posterior sternal margin, incline slightly in a mesial direction, push in 4 to 5 cm. After some

blood is aspirated slowly make the injection of 1 cc. adrenalin. Movements of needle due to cardiac contractions are favorable. One reaches the right ventricle by this method. By this site injury of internal mammary artery and pleura is avoided. The fine needles largely preclude injury of coronary vessels or conducting system.

Schwartz and Jezzer (1932) consider that the drug may be life saving where the seizures are due to ventricular slowing (as is always the case in true Adams Stokes syndrome) but that it is contraindicated when they are the result of ventricular fibrillation. There is general concurrence in this opinion. Levine (1937) says that in the latter instances quinidine is indicated both from a theoretical and a practical point of view. Surely the opportunity to try it must present itself rarely indeed.

Ephedrine Sulfate.—There have been several reports of success with this drug in a single or small series of cases but doubtless it has failed in many more unrecorded instances. Gilchrist believes it worth a trial in the attempt to lessen the incidence of seizures. It was successful in 4 of his 6 cases. Easby suggests that because of the drug's tendency to cause urinary retention in some individuals the starting dose be only $\frac{1}{2}$ grain (0.008 Gm.) full dosage is $\frac{3}{4}$ to $\frac{1}{2}$ grain (0.024–0.03 Gm.) three or four times daily by mouth.

Barium Chloride.—This drug was introduced a number of years ago in the attempt to increase the irritability of the ventricles. Cohn and Levine obtained striking effects in their 3 patients using $\frac{1}{2}$ grain (0.03 Gm.) doses three or four times daily by mouth. Such results have been had by others but there has certainly been at least an equal number of failures. For example Parsonnet and Hyman (1930) were unsuccessful in 8 consecutive cases. A large series as Adams Stokes syndrome goes. The drug is now being used in somewhat larger doses than those originally employed—up to as high as 5 grains (0.3 Gm.) three times daily in some instances according to Gold (1940). In Gilchrist's experience these larger doses have not been harmful but it may be worth noting that in Graham's (1934) case of accidental ingestion of an enormous amount of barium chloride crystalline sodium sulfate in dosage of several teaspoonfuls by mouth proved an effective antidote.

Other Drugs.—Upon the whole the use of thyroid substance or thyroxin which causes tachycardia in the normal individual has been very disappointing in this malady. However Easby *et al* (1935) have reported favorably using $\frac{1}{2}$ to 3 grains (0.03–0.2 Gm.) of thyroid extract daily and Parker and Willius (1938) have referred to its use still more recently. Vasodilators have been recommended to reduce peripheral circulatory resistance and thus aid the handicapped myocardium—such drugs as aminophylline and the nitrites as used in angina pectoris. Lueh (1938) thought that metrazol was effective in 2 of his 4 cases. Sigler (1939) found his 4 patients definitely improved by intravenous injections of 50 cc. of 50 per cent dextrose solution. Starling (1938) felt that the intravenous injections of 10 cc. of 5 per cent peptone which he used in his patients were beneficial. His report of the fifteen years course of this case is very interesting.

CHRONIC NONVALVULAR HEART DISEASE

(The Failing Heart of Middle Life, Myocardosis)

A very large proportion of the patients in whom symptoms of cardiac derangement have developed after the age of forty may be classified under this present head. They have neither endocardial, pericardial, valvular nor coronary lesions and their disability seems to depend entirely upon inefficiency of the muscle. The cases may be placed more or less satisfactorily in Christian's three groups: (a) Patients who at any age complain of great exhaustion or of palpitation following slight exertion. They do not have true dyspnea but experience uncomfortable sensations in connection with respiration, perhaps have some substernal distress, and are sensitive to pressure in the region of the apex and their heart rate is easily accelerated. Examination reveals a normal heart, but with perhaps a few extrasystoles and a rather tapping pulse, there are no evidences of past or present edema or passive congestion. Usually an adequate cause for the condition can be found in antecedent infections in debilitating diseases with a too short convalescent period or in occupational overfatigue together with worry and loss of sleep. (b) Patients, usually past forty, in whom the chief departure from normal is in the size of the heart, hypertrophy often being very marked. Just what causes this hypertrophy, and why the hypertrophy should result in dysfunction, has never been satisfactorily explained. There may or may not be a soft to loud systolic murmur best heard at the apex, but it is important to bear in mind that the mitral insufficiency is the result and not the cause of the myocardial insufficiency. This cardiac enlargement would seem to mark the beginning of a train of events which practically always ends in cardiac decompensation. (c) Relatively uncommon are the patients with true chronic myocarditis. At autopsy there may be found small foci of perivascular infiltration with lymphocytes and plasma cells, or, far less frequently, a focal or a widespread fibrosis with definite evidence of injury to the muscle fibers. These chronic myocarditis cases are said to be indistinguishable clinically from those above described, in which there is hypertrophy and no other change.

THERAPY

Myocardial Fatigue—The practitioner who will assure patients with simple myocardial fatigue, those described in group (a), that they have no heart disease and are sure to get well renders a real service to mankind. For these patients form a large class of chronic invalids who burden their friends with their weak hearts and all because an incorrect diagnosis was made in the beginning. Rest and reassurance, with a gradual return to full physical activity is all that is needed in these cases. Indeed, their easy curability is the chief mark by which they may be distinguished from neuro-circulatory asthenia previously discussed. Christian says that these hearts which are normal in size, sounds and function offer the striking example of when digitalis should not be used, not that it is harmful but because it is not beneficial. Yet many of these patients are found to be entirely dependent upon daily doses of digitalis which would be inadequate if the drug was actually needed or they may take it only when their heart is "bad" getting immediate relief—all of which goes to show, says Christian, that for such

patients digitalis in such doses is not a cardiac medicine but one that works directly on the mind."

Hypertrophy and Chronic Myocarditis—These cases, those described in (b) and (c) above are said often to present very considerable diagnostic difficulties by reason of the fact that a regular rhythm is frequently maintained, but decompensation here, as in other types of heart failure indicates digitalis—Christian has long been stoutly championing this viewpoint which has been substantially supported in recent years by the observations of Gavey and Parkinson (1940), Wood (1940), and Larson and Hallock (1940). For example, Gavey and Parkinson compared the drug's action in 65 cases of decompensation with normal rhythm and 30 cases with auricular fibrillation. 60 per cent beneficial results were obtained in the former and 70 per cent in the latter cases, Wood obtained a beneficial effect in 90 per cent and Larson and Hallock in 70 per cent, of their smaller series of regular rhythm cases. For the details of digitalis therapy the discussion of congestive heart failure must be read.

In cases of cardiac enlargement, even though there be no signs or symptoms of decompensation, Christian (1933) also uses digitalis continuously in amounts just short of toxicity and feels certain that there is no reason to fear deleterious effects from such therapy.

CONGESTIVE HEART FAILURE

This is the state of broken compensation in which the heart is no longer able to perform the amount of work necessary if the body as a whole is to maintain a condition of normal activity. When first seen if the decompensation is severe, the patient is in bed, usually propped up on several pillows, has a depressed though anxious expression (perhaps even pronounced symptoms of mental disturbance), is breathing with difficulty, may or may not be cyanotic (in mitral disease the cheeks are often flushed whereas pallor is characteristic of aortic lesions), and has a rapid and usually arrhythmic heart. Edema of the lower extremities is usually present, and perhaps even anasarca with fluid in the serous cavities. The liver is engorged, the kidneys congested, and the urine is scant and contains albumin and casts. Often there are rales at the lung bases and congestive cough, sometimes "cardiac asthma," and occasionally, and especially in aortic disease, complaint of cardiac pain. Slight fever is not at all infrequent even in the absence of infectious processes. Decompensation such as this may result from a recently acquired or a long standing valvular lesion, or it may be a part of the picture in chronic non-valvular heart disease previously described. Obviously, a more detailed description of the physical findings in the various types of heart disease has no place in this book, nor is it in order to describe the premonitory symptoms by which the onset of complete decompensation may be recognized. Whether heart failure is primarily of the 'forward' sort, in which the fault would be in diminished cardiac output, or of the 'backward' type with distress resulting predominantly from back pressure, remains undecided though the question is of considerable importance.

THERAPY

Rest—Rest in bed is usually self imposed in cases of severe failure, though it is astonishing how long individuals of indomitable will are some times able to keep on their feet, it is of course imperative if cure is to be accomplished that the patient be placed in bed even though he is able to repose there only in a sitting posture. This is by no means the same thing as saying that every patient with decompensation will show direct profit by being sent to bed, for the factors of arrhythmia, edema and congestion, etc., are grave perpetuators of the broken-down state, but it does mean that, other things being equal, the patient who takes to his bed early and rests while he is in it, has the best chance of recovery, be his decompensation slight or great. However, as Levine (1940) points out, there are instances in which putting the patient to bed may cause a shift of some of the fluid from the dependent extremities, where it is relatively harmless, into the lungs with the possibility of establishing serious congestion there before digitalis can begin moving the fluid to the kidneys. Individualization of treatment should therefore be the watchword here as everywhere.

To the end of providing complete rest, even though the patient be one of the minority whom it may seem desirable to keep up in a chair with the legs hanging down in the beginning it is often advisable to employ sedatives (see Insomnia). Sometimes the best sedative is an analgesic—morphine, dilaudid, codeine for a few doses. Some patients are relieved by the ice bag applied to the hypochondrium.

Diet—In the beginning of an attack of decompensation the patient will not be interested in food but in a few days especially after the use of sedatives and analgesics has been stopped, the matter of dietetics needs to be faced. Some physicians like to keep the patient on the radical Karell diet (a glassful of milk at 8 A.M., noon, 4 and 8 P.M., and no other food or fluid) as long as he will take it, which is usually no more than a few days and then add small but frequent feedings of such substances as vegetable purées, lightly cooked red meats, chicken, fish, well baked breads and well-cooked potatoes and green vegetables, rice, tapioca, custards and ice cream. All this may perhaps be summed up by saying give the patient only milk in the beginning and thereafter small frequent feedings of a general diet. Of course in these vitamin-conscious days one should look into the possibility of a preceding deficiency and make such corrections by supplementary vitamin therapy as may be indicated. Salt is usually reduced to the minimum in the diet and fluid often restricted to 1 quart (liter) per day, but it does not seem advisable to permit the patient to be excessively thirsty or have the discomfort of a dry mouth. Levine (1940) points out that when there has been excessive sweating, or if the nonprotein nitrogen in the blood is rising it may be necessary to force fluids for a short period. Most clinicians believe that the obese patient with heart failure should be reduced.

Rapid Digitalization by Mouth—The response of a decompensated heart with auricular fibrillation to digitalis is very spectacular. The pulse is decreased in rate and increased in volume, diuresis is established and edema decreases, dyspnea, cyanosis etc., diminish—in short, compensation is reestablished and the patient's life is saved. In nonfibrillating cases, of the sort earlier described as "chronic nonvalvular heart disease," the reduction in rate is not so pronounced because the increase has not been as great, but the

other evidences of powerful action are shown I think that Levine's (1940) recent authoritative statement should be placed here *in toto* "It must be borne in mind that digitalis is indicated in congestive heart failure whether the blood pressure is high or low, whether the rhythm is regular or grossly irregular, and whether the rate is rapid or slow. It is to be used in myocardial or in valvular disease, whether fever is or is not present, and whether the basal metabolism is normal or elevated. The results to be expected may differ under varying circumstances but the indication for its use remains the same." The study of Blumgart and Altshuler (1939) indicates that digitalis, in somewhat reduced dosage, may be safely employed for the correction of congestive failure in the presence of partial heart block.

In 1915, Eggleston revolutionized digitalis administration by the demonstration that the body weight of the patient may be utilized for the estimation of the approximate total amount of the drug which will be required to obtain its therapeutic effects. 15 minims (1 cc) of the tincture, or $1\frac{1}{2}$ grains (0.1 Gm) of the leaf, for each 10 pounds of body weight. Thus, in a patient weighing 150 pounds, the approximate dose at which full effect may be expected would be 225 minims (15 cc) of the tincture and 22½ grains (1.5 Gm) of the dried leaf—figures which are arrived at by the simple procedure of inserting in the figure representing the patient's weight in pounds one decimal from the right for the tincture and two decimals from the right for the leaf. However, while yielding full credit to Eggleston for leading the profession into bolder digitalis therapy, many physicians have come to doubt the value of utilizing the body weight for determination of the dose, feeling that this affords a false sense of security on the basis of a formula which can only be approximately correct. Furthermore, the following pertinent questions, which are not easy to answer, are often asked by the general practitioner: How many patients, as seen in the home, have an accurate knowledge of their normal weight before the onset of edema? How are we to weigh them in the home? And if we succeed in doing so, how much allowance must be made for retained fluid which is not to be included in the individual's weight?

Some years after his original contribution Eggleston and his associates proposed the modification of the weight method which has now come to be almost universally employed, namely, to adopt the original Eggleston dosage for the 150 pound man—22½ grains (1.5 Gm) of leaf or 225 minims (15 cc) of tincture, as the average effective total dosage, portions of this total to be administered at intervals according to an arbitrary scheme. Many such schemes have been published, I have formerly filled my pages with them but now I believe that nothing can serve the reader better than to state here the simple plan followed by Christian (1937), of Boston for patients with marked decompensation not having received digitalis in any form within the past week, the initial dose should be 7½ grains (0.5 Gm), to be repeated in four hours, and usually again four hours later, the patient thus receiving 22½ grains (1.5 Gm) in the first eight hour period. Thereafter, doses of $1\frac{1}{2}$ to 3 grains (0.1–0.2 Gm) may be given three times daily until therapeutic effect is achieved or evidences of toxicity appear. In this scheme the foregoing initial large doses should be increased for cases of greater severity and for very large patients. Conversely, for less markedly decompensated patients, and for small patients, these initial doses may be curtailed or abandoned. Abandonment of the large initial doses is particularly indicated when the patient previously has been getting digitalis in any considerable amount.

In the above it is assumed that a biologically standardized leaf (see below), in tablet, pill or capsule form, will be used. Biologically standardized tincture, which in the opinion of many observers is perhaps not quite so good may be substituted in dosage ten times as great, *i e.*, 75 minims (5 cc) for the high initial doses, and 15 to 30 minims (1-2 cc) for the smaller doses. Significant deterioration of the leaf preparations when kept dry, or of the tincture when tightly corked, does not take place. The prescribing of the tincture in drop dosage is open to two serious objections, first, that droppers vary greatly in the amount of an alcoholic preparation they will deliver, and second, not all patients or their attendants at home are sufficiently disciplined to use a dropper with consistent integrity. Perhaps the better way of prescribing the tincture (but why use it at all?) is in a bottle with a suitable vehicle to bring the 15 minim (1 cc) dose up to 75 minims (5 cc). A graduated vial prescribed with the medicine will then ensure accuracy in dosage. In the following prescription, the vehicle chosen is one containing no hydrochloric acid, which has given all vehicles their undeserved reputation of causing deterioration in the tincture, and contains about the same amount of alcohol as the tincture, it makes a mixture as little disagreeable as may. If the teaspoon the patient uses after he breaks the vial contains exactly 5 cc he will still obtain 1 cc of tincture of digitalis in each dose, if not, and he will only continue to use the same spoon, the error will be at least a constant one.

R _x Tincture of digitalis U.S.P.	3xiii	60 0
Iso-alcoholic elixir (N.F. VI)	3viij	250 0
Label it or more teaspoonsful (5 cc) as directed.		
Dispense a 3ss (15 cc) measuring vial		

Comparison of Preparations—Digitalis of the *US Pharmacopoeia XI*, in official use since 1930 is 50 per cent stronger than that of the previous pharmacopoeia and therefore 10 minims of present tincture, for example, are equivalent to 15 minims of the previous tincture. Many men are much exercised about this and maintain that vigorous measures must be taken to acquaint the profession with these facts so that dosage may be adjusted accordingly. I do not share this perturbation at all, for two reasons. (a) the requirements of the *Pharmacopoeia* itself are not by any means rigid since a 40 per cent range is allowed between the weakest and the strongest preparations meeting the requirements, (b) Gold and Cattell (1941), studying a number of the tinctures in most popular use, found that some were three times as potent as others though all bore the *USP XI* label. The fact is that when a man digitalizes his patient by a broken dosage method as outlined above he has rather good control of the situation and can usually adjust dosage to meet the conditions both with regard to the patient and the preparation of digitalis at hand. The thing to be highly desired and striven for, as Gold points out, is the preparation of a crystalline active principle which will not require biologic standardization. Such an agent is not yet available though progress is being made toward its development. Studies with the crystalline material known as "digitaliac nativelle," and with the product, "digitanid," which is a mixture of three crystalline glucosides ("lanatosides") obtained from digitalis lanata, are being watched with much interest but it does not seem to me that the time has yet arrived to discuss their use in a book of this sort (the interested reader will find the following references in

he Bibliography Adams and Gregg, 1940, Fahr and Ladue, 1941, Batterman *et al*, 1941)

Modification of Dosage for Rapid Digitalization of Children—Taussig (1935), at Johns Hopkins Hospital offers the following dosage scheme for a child weighing 50 pounds (22.7 Kg) give $1\frac{1}{2}$ grains (0.1 Gm) as test dose, two hours later, 3 grains (0.2 Gm), six hours later 3 grains again, and six hours thereafter $1\frac{1}{2}$ grains. If not digitalized at the end of the twentieth hour, continue $1\frac{1}{2}$ grain doses every six hours for 3 or 4 more doses provided there are no signs of toxicity, and then place the child on maintenance dosage. Walsh and Sprague (1941) found that good responses to the drug were obtained in only about one half of their 33 children with rheumatic heart disease which seems to be about average experience.

Rapid Digitalization by Intramuscular Injection—Regarding the proprietary preparations of the purified glucosides of digitalis one may consider them to have absolutely no advantages over the leaf when given by mouth, this has been quite convincingly shown in the studies of Stroud *et al* (1934). In an occasional case in which congestive vomiting is very severe in the beginning and there is some reason for not giving strophanthin intravenously (see below), it may be advisable to use one of these preparations by intramuscular injection until the leaf will be retained when given by mouth. The standardized $1\frac{1}{2}$ grain pill, tablet or capsule of leaf contains 1 cat unit. The following amounts of Council accepted proprietary preparations for injection are equivalent.

Digitalis leaf	$1\frac{1}{2}$ grains (0.1 Gm)	1 cat unit
Digalen injectable	2 cc	1
Ampules of digitaline	2 cc	1
Digitalan ampules	1 cc	1

[I do not know of any authoritative studies showing these injectable preparations to be as reliable as the leaf. Eggleston (1940) says he has found very little occasion for using them. Evans (1940) study, in which the superiority of the leaf to the injectable preparations was shown comprised the comparison of these agents in only 18 patients and therefore does not suffice as a basis for conclusions.]

Slower Digitalization and Maintenance Dosage—In mildly decompensated bedridden patients who are not seen by the physician at short intervals it is neither necessary nor wise to employ the large dosage described above. Also in ambulatory patients seen only at relatively long intervals it is very dangerous to employ such dosage. In these cases a safe rule would seem to be that $1\frac{1}{2}$ grains (0.1 Gm) of leaf, or 15 minims (1 cc) of tincture, once twice or three times daily will suffice in most instances. The theoretical amount required to maintain saturation, based upon Pardee's studies of elimination, would be $2\frac{1}{2}$ grains. The fact, however, that decreasing need for circulatory improvement indicates the necessity to be alert for opportunities to reduce maintenance dosage. The study of Weinstein *et al* (1940) indicates that the tendency to prevent ventricular acceleration during exertion and emotional stress is one of the most valuable results of digitalis administration in maintenance dosage.

Taussig (1935) slowly digitalizes the child of 50 pounds (22.7 Kg) as follows: $1\frac{1}{2}$ grains three times daily at six-hour intervals (8, 2 and 8 o'clock).

or 10, 4 and 10 o'clock) for three days, fourth day, a dose in the morning and if necessary, at night, thereafter maintenance dosage, which would probably be $\frac{1}{2}$ grain (0.05 Gm) daily, six days a week.

Digitalis by Rectum—Levy's studies of some years ago, indicating the feasibility of rectal administration, have been amply confirmed, but nowadays when congestive vomiting makes oral medication impossible in the beginning proprietary preparations are likely to be given by injection. However, they may be given rectally in the same dosage as would be given intramuscularly (see above), preceding the administration by a cleansing enema, and washing the drug in with about 1 ounce (30 cc) of saline solution. For convenience the total daily dose may be given at one time. Tincture of digitalis may also be used, but the necessary dilution to avoid excessive irritation by the alcohol (4 cc of tincture in 100 cc of water) is likely to make the bulk too great for easy retention.

Intravenous Strophanthin (Ouabain)—When digitalis is given by mouth full effects are not obtained under twelve to twenty four hours, but beginning effects may be seen in two to four or five hours, thus a life saving degree of digitalization is accomplished quite rapidly enough by oral administration in the vast majority of cases. In the occasional case where speedier action is thought necessary, crystallized ouabain, the glucoside obtained from *Strophanthus gratus*, is the preferred preparation (In England, *S. lombe* is used and *S. emini* is being investigated—Bedford, 1935). The commercial ampule contains the drug in buffered solution in hard glass under which circumstances it is stable. Wychoff and Goldring worked out the dosage at Bellevue Hospital a number of years ago in patients having received no digitalis in the preceding two weeks, the initial dose is 1/120 grain (0.5 mg), Eggleston (1940) advises that the dose be placed in 10 cc of fluid and five to ten minutes be allowed for injection. Beginning effect is observable in a few minutes in average cases and full effect in about an hour. Most conservative men nowadays give only one dose, or at most do not repeat the dose in less than twenty four hours, but Wychoff felt that in the presence of marked auricular fibrillation, where therapeutic effect can be easily noted, several subsequent doses of 1/600 grain (0.1 mg) may be used at half hour intervals after the initial large dose. Eggleston (1940) prefers one- to two hour intervals if these subsequent doses are to be given. Of course the sole object of ouabain intravenous therapy is to save the life of the patient until peroral therapy may be begun, but just when to begin the oral therapy under these circumstances and how much of the drug to give have been important and not entirely settled questions. Recently, however, Batterman et al (1940), also of the Bellevue group, have shown that the following plan is feasible: (a) give simultaneously 1/120 grain (0.5 mg) of ouabain intravenously and 10 grains (0.6 Gm) of digitalis leaf by mouth (6 grains [0.4 Gm] for those under 125 pounds edema free weight, 10 grains [0.6 Gm] for weights between 125 and 175 pounds, 13 grains [0.8 Gm] for weights above 175 pounds), (b) no further medication for twenty four hours, (c) determine maintenance dosage by trial thereafter. This is only a single study but will doubtless serve as model for others and should give some guidance to the puzzled practitioner.

Clinical Toxicology of Digitalis—By full digitalization is meant the administration of digitalis until its full therapeutic effects are obtained, at which time there usually also appear mild symptoms of toxicity. The phys

ician should familiarize himself with *all* the signs of toxic action and not be content to recognize merely the most familiar ones, such as nausea, drowsiness and excessive slowing of rate. The following is the list, arranged for convenience in memorizing.

<i>Gastro-intestinal</i>	Nausea, loss of appetite, vomiting, diarrhea
<i>Circulatory</i>	Coupled rhythm, partial or complete heart block, simulation of any of the other spontaneous arrhythmias, diminution in secretion of urine, cold extremities
<i>Nervous</i>	Headache, drowsiness, mental confusion, visual disturbances
<i>Allergic</i>	Urticarial or scarlatiniform rashes, asthma, angioneurotic edema, etc. (all of these reactions are extremely rare)

To single out certain of these symptoms as invariably marking complete digitalization is erroneous and dangerously misleading. Gastric symptoms do not occur in all cases even if the patient is seriously poisoned, and an initial stimulation of the vomiting reflex may be succeeded by depression of the same, so that to rely greatly upon nausea and vomiting as measures of the degree of cardiac poisoning may be a very dangerous policy. Nor is the typical slowing of the heart always seen. To consider disturbances of vision as among the invariable signs of full digitalization is also misleading, for flickering disturbances are perhaps more often absent than present when digitalization is reached.

Excretion of digitalis in the milk has not been demonstrated and almost certainly does not occur; there is therefore probably no danger to the infant if the nursing mother is digitalized, but even so I should think that a bit of extra watchfulness would not be amiss.

Digitalis Combined with Other Drugs—It has been shown to be dangerous to use the following drugs when digitalis is being taken: epinephrine, atropine (McFarlane and Masson, 1927, animal studies only), ephedrine (Seevers and Meek, 1935, animal studies, Johnson and Gilbert 1931, clinical), calcium (Gold and Edwards, 1927 and 1937, Lieberman 1933, Golden and Brans 1938, and others—animal studies with which Smith *et al.* 1939, disagree, Bower and Mengle 1936, clinical).

Digilanid and Digitaline Nativele—See under Comparison of Preparations on a preceding page.

Squill Derivatives—Squill is much older in the therapy of heart failure than is digitalis but has been justly overshadowed by the latter drug. Recently, there is some stir of interest in certain glucosides obtained from the crude drug, but I fail to see the advantage of cluttering up treatment with these new substances, since they have a toxicity practically identical to that of digitalis, and a therapeutic action in no wise superior so far as has yet been shown. The reader may find the papers of Carr and Mayer (1930), and Maher and Sittler (1936), of interest. The Council has accepted the following: (a) Scillaren, available in tablets of 1/80 grain (0.8 mg.), and a solution with the same amount per cc. Dosage is said to be 1/40 grain (1.6 mg.) orally three or four times daily until compensation is established or minor toxic symptoms appear, dosage for maintenance of compensation 1/80 grain two to four times daily. (b) Urginin, available in tablets of 1/120 grain (0.5 mg.) Dosage is said to be 3 mg. daily in divided doses at six hour intervals until effect is observed, maintenance dose, 0.5 mg. daily. (c) Scillaren B is designed for intravenous administration, available in ampules

each cubic centimeter of which contains the dose, 1/120 grain (0.5 mg.), which is not to be repeated within twenty-four hours.

Venesection—Since venous pressure is recognized as being elevated in congestive heart failure, periodic waves of enthusiasm pass through the profession for the withdrawal of 400 cc or more of blood. So-called 'bloodless' venesection is also practiced constricting the four limbs close to the trunk tightly enough to prevent venous return, the hope being to relieve the heart of a portion of its load without actual loss of blood, which it must be admitted the patient does not always bear with perfection. Few exact studies of the value of either of these measures are available, but Brams and Golden (1935), gave up the 'bloodless' method after convincing themselves of its worthlessness, and having followed many patients after actual venesection, they are skeptical of its value also. "It is possible that our patients had very little cardiac reserve, but we are inclined to rely on digitalis, sedatives and diuretics and to advise venesection only occasionally in right-sided cardiac failure." Levine (1940) seems also to feel that venesection is not often indicated but he finds that sometimes in cases of marked engorgement of the liver, acute pulmonary edema or paroxysmal dyspnea, a bleeding will produce prompt relief.

Oxygen—Used as in pneumonia, oxygen therapy seems to have passed the peak of its popularity. The difficulties in arriving at a true judgment of the worth of the measure are very great. Katz *et al* (1932), after a study of the literature and their own cases, felt that oxygen's role would probably prove to be to add to the comfort of patients who have definite pulmonary complications—congestion, consolidation, infarction, edema, etc. "Miracles are not to be expected, and in the presence of prolonged, advanced, progressive cardiac disease, as is true also of other available therapeutic measures, oxygen cannot achieve the impossible."

Diuresis—Usually rest and digitalis will in themselves result in considerable diuresis, but where edema is marked, as it is most likely to be in failure occurring in individuals with chronic nonvalvular disease with or without hypertension and arrhythmia, more direct diuretic measures are often productive of excellent responses. Indeed, the diuretic drugs not only promote fluid loss but in many instances also effectively relieve dyspnea. The studies of Friedman *et al* (1935) show that under favorable circumstances not only may the load on the heart be decreased but there may also occur an increase in the organ's ability to carry its load, these effects on cardiac output are not constant, however. Fluid in the abdominal cavity and subcutaneous tissues seems to be equally well moved by the diuretics, that in the pleural cavity much less so. Lack of distensibility of the thoracic cage makes the latter much more disturbing to the patient also. I am sure that many agree with Christian (1936) in his advocacy of removal of this fluid by thoracocentesis as soon as any considerable dulness is detected on chest percussion. Volini and Levitt (1940) find that cerebrospinal fluid pressure is reduced by the effective employment of diuretic drugs. Levine (1940) finds that in some instances effective diuresis is obtained only after abdominal paracentesis has released pressure on the renal vessels. In a few instances of resistant dependent edema, Southey tubes may be of value, see also Nephritis.

Mercurials—These are the most effective diuretics but have the dis

advantage that, with the single exception noted below, they must be given parenterally—preferably intravenously, permissibly but probably painfully intramuscularly, and never subcutaneously because of the certainty of irritation and the possibility of sloughing (Marks, 1939, says that the prompt injection of sodium cacodylate solution into and about the extravasation prevents pain and necrosis) Experience has shown that they act better when the body reaction is tipped toward the acid side, for which purpose various salts have been utilized, of which the three following are the most effective ammonium chloride, ammonium nitrate, and potassium nitrate, Keith (1925-1935), who introduced this preliminary acidifying therapy, prefers the potassium salt The consensus is that any one of these salts must be given in amounts of 90 to 150 grains (6-10 Gm) distributed throughout the twenty four hours They alone will often induce diuresis but not nearly so reliably or satisfactorily as when followed by a mercurial Since the degree of induced relative acidosis is greater on the second and third days than subsequently, a satisfactory method is to give the salt only for two days before and on the day the mercurial is given and then to repeat this program when next diuresis is desired These salts are very irritating to the gastric mucosa, Hayman (1936) points out that if they cause much vomiting, the resultant swing toward alkalosis will defeat the purpose for which they were given The following are probably satisfactory prescriptions containing 15 gram (1 Gm) of the drug per teaspoonful

R Ammonium chloride	℥j	80 0
Arose water	℥j	80 0
Syrup glycyrrhiza to make	℥iv	120 0
Label 1 or more teaspoonfuls well diluted as directed		
R Potassium nitrate	℥j	80 0
Syrup glycyrrhiza to make	℥iv	120 0
Label 1 or more teaspoonfuls well diluted as directed		

Instead of these salts, Weigand (1935) and a few others have used 10 cc of 20 per cent sodium dehydrocholate (decholin) solution, given intravenously at the time of giving the mercurial

The mercurial drug is usually given in a single dose, to be repeated in a few days or weeks as needed, apparently effectiveness is not lost no matter how often the medication is repeated Evans and Paxon (1941) feel that for the patient confined to bed, injection every third day is probably the most satisfactory routine Best practice is to administer the dose early in the morning in order to have the most vigorous diuresis over before sleeping time at night Merbapben (novasurol), the earliest of these drugs but now discarded, often gave rise to rather serious gastro intestinal and renal reactions, but reactions of any sort are very rare with the preparations now in use Poll and Stern (1936) point out, however, that a syndrome characterized by weak restlessness, mental symptoms, perhaps coma and death, and easily combated by oral administration of salt water, may arise through depleting the system of water and sodium chloride Klinghofer (1941) believes that this state is seen much more often than meager reports would indicate, in his 3 cases it followed persistence in the use of diuretic measures after edema had disappeared Price (1939) has seen severe attacks of gout apparently in close association with salyrgan diuresis in 5 of his

patients *A N R Preparations* (1941) (a) mersalyl (salyrgan), 1 to 2 cc intravenously, (b) mersalyl (salyrgan) theophylline solution, 1 to 2 cc intravenously (said to be less toxic locally if extravasated into the tissues and also to be often more effective than mersalyl), (c) murcurin, the same drug as the above, supplied in suppository form in which it is said to be fully as effective as when given intravenously, and of course much easier to administer (however, Brightman and Batterman, 1940, find that it is only about 60 per cent dependable and may occasionally cause local discomfort and burning) Batterman *et al* (1941) find that in a single dose of 5 tablets, a mersalyl (salyrgan) theophylline preparation they are studying is very effective when given by mouth, the preparation is not as yet commercially available I believe

Xanthines—These drugs are often effectively diuretic but less uniformly so than the mercurials over which they have the advantage, however, of being administered by mouth The list and methods of use are in Coronary Disease, as diuretics it is customary to employ somewhat larger doses than there stated—unfortunately, more of the unpleasant effects are seen also Hayman (1936) finds theophylline (theocin) best and theobromine next best Strauss (1936) and Christian (1936) also favor theocin, which the latter gives in 2 doses of 5 to 7½ grains (0.3–0.5 Gm) with ½ glassful of water at 7 and 10 A M, in order to obtain diuresis at seasonable hours He prefers not to repeat the administration in less than forty eight to seventy two hours Walsh and Sprague (1941) used the xanthines with good effect in children between three and fifteen years of age dosage ranging between 3 and 5 Gm divided into three equal doses during the day, they found diuretin suitable for rectal administration in doses of 1 to 2 Gm in tap water three or four times daily

Urea—Crawford and McIntosh a number of years ago found this drug useful but it has not been much employed for the reason that it is objectionable in taste and doses of ½ to 3 ounces (15–90 Gm) must be given daily However, Hayman (1936) reports its use in alternate periods of three to five days of administration and omission, with resultant good diuresis in 83 per cent of the cases and no toxic effects Of course it is not to be used if the patient is already retaining nitrogen Urea may be stirred up in water, or prescribed in the following form, in which 1 teaspoonful will contain 15 grains (1 Gm)

Rx Urea	℥i	℥o
Acacia powder	℥ij	℥o
Syrup of cinnamon to make	℥iv	℥o
Label 1 or more teaspoonfuls well diluted as directed		

Catharsis—Cathartics are not much used in these days of proper digitalis and diuretic therapy, but occasionally they still help to "wring out" the liver For a list of saline cathartics, see Index

Quinidine—The principal matters pertaining to this drug are discussed in connection with auricular fibrillation unassociated with congestive failure By common consent nowadays the routine use of the drug is not necessary in advanced organic heart disease with fibrillation, since the pulse can usually be reasonably well slowed even though not regulated by digitalis Indeed, Brill (1937) points out that abolishing the arrhythmia may be undesirable, for some of these hearts seem to derive an advantage from the

auricular fibrillation, and the temporary regulation of the rate with quinidione may offer no benefit commensurate with the degree of risk involved in the use of the drug. However, in certain otherwise hopeless cases where all other means of therapy have failed, the drug may occasionally be quite helpful. And there is also another class of patient, as referred to by Kohn and Levine (1935) and seen occasionally in most practices, that is sometimes remarkably helped by quinidione—individuals whose chief complaint is severe palpitation which remains intractable even after thorough and maintained digitalization. I should not omit to say, however, that Weisman (1936), of Minneapolis, still apparently favors the attempt to correct the arrhythmia in most cases. It is interesting to note that he uses much smaller doses than those discussed in the article on auricular fibrillation *per se*. Following digitalization, and while continuing the drug, his plan is to give 1 dose of $1\frac{1}{2}$ grains (0.1 Gm.) the first day, 2 such doses an hour apart the second day, 3 on the third, 4 on the fourth, 5 grains (0.2 Gm.) 10 3 hourly doses on the fifth, 4 such doses on the sixth, 5 grains (0.3 Gm.) for 3 doses on the seventh, and 4 such doses on the eighth. Thereafter he increases dosage rapidly to 10 grains (0.6 Gm.) three times daily at hourly intervals and gives up the attempt if normal rhythm is not achieved in a few days on these full doses.

Treatment of the Post-Failure Period—Every effort should be made to build up the child's general health and especially his exercise tolerance through supervised play, etc. Such things are not easily accomplished under supervision of the parents and therefore whenever possible the child should be sent to a convalescent home or a cardiac camp. For the adult, graded exercises, hydrotherapy and massage are held by the majority of physicians to be of considerable importance if the cardiac reserve is to be maintained or built up, though there are dissentient voices. For all who can afford it a long sojourn at a spa is ideal—preferably a jolly, dressy one with a hand in the open and perhaps a race course not too distant.

CORONARY DISEASE

Angina Pectoris—Angina pectoris is a serious malady that is wide spread throughout the world, affecting everywhere men much more often than women. It has probably been recognized since classical times, but the first complete description was that of Heberden before the Royal College of Physicians in London, in 1768. The disease seems to affect especially the intellectual classes upon whom rest the political, professional and business worries of the world, but it is by no means unknown among purely physical laborers. There is now general agreement that the individual attack reflects a transitory period of undernourishment of a portion of the myocardium. The onset is usually in the late fifties, fewer cases occurring in the forties, and cases in individuals under thirty being extremely rare. The coincidence of angina and anemia, functional nervous and mental disturbances, gall-bladder disease and particularly diabetes mellitus is beginning to be studied statistically. The symptoms are very typical, and it is upon them and the history that diagnosis must be based, for there are no constant and reliable physical signs or laboratory findings. The anginal attack is a sudden viselike

gripping of the thorax, usually centering behind the sternum, with pain that is more often crushing than knifelike, and accompanied by an agonal sense of impending death. When the pain radiates it is nearly always into the left shoulder and down the left arm, but sometimes it extends up into the jaws also. Such an attack may be precipitated by unusual exercise or, in the more severe cases, by the most ordinary movements of the body, in some cases emotional stresses or crises are the more potent causes, and there are some individuals who experience most of their attacks at night in bed. The paroxysm is characterized also by one other conspicuous feature, the immobility of the patient, he may elect to stand or to sit bolt upright (he rarely reclines), but whatever his posture he retains it fixedly, rarely even emitting a groan despite his pain, until the attack has passed. The paroxysm may last only a few seconds or it may persist for several minutes, if it lasts more than one quarter hour, the observer does well to suspect coronary occlusion, or that he is dealing with one of the many atypical or pseudo anginas. Indeed, classification of cases into "functional" and "coronary" types is usually possible and is of considerable prognostic aid, for patients in the former group may round out a full term of life after their first seizure, whereas those in the latter are likely to do so only if their cardiovascular and mental inheritance is exceptionally good. There are many criteria for differentiation of these types, but the two most important points seem to be (a) that attacks of 'functional' angina bear only a most capricious relationship to effort, and (b) that true "coronary" cases are relatively infrequently encountered in women, especially in women with normal or low blood pressure. Numerous reports on periods of survival have now fairly well fixed the following as about what is to be expected in true "coronary" cases: (a) death within four to five years after the first attack, (b) sudden death in half the instances usually from coronary occlusion, (c) slower death from coronary occlusion in three fifths of the remaining patients, (d) death in the last small portion from the diseases of their age period.

Coronary Occlusion—The correlation of bedside and pathologic findings in coronary occlusion, with the resultant recognition of it as a definite clinical syndrome, has taken place only in this present century. Thrombus formation is the commonest cause of interference with the coronary circulation. The interested reader is referred to the fine studies of Blumgart *et al* (1940) on the relationship of the clinical and pathological findings in coronary disease, which it does not seem within my province to review here save to say that in general it seems conclusive that death occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis, or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs. As in angina pectoris, the victims are usually past fifty years of age, at least half the men and practically all of the smaller number of women are said to be hypertensive and the women also usually diabetic. There is increasing evidence that the incidence of attacks is greatest in winter. Except when death is sudden, the salient features of acute occlusion are the following: (a) severe substernal or upper abdominal anginoid pain, sudden in onset but of long duration (though according to Steiner [1940] there is a characteristic rhythmicity and periodicity of the pain during the attack), (b) pinched, ashen gray or very pale facies often associated with a feeling of impending death, but usually without the fixation in position so charac-

teristic of angina pectoris, (c) cold sweat and cold extremities, (d) acute emphysematous distention of the lungs with dyspnea or orthopnea and moist crackling râles at the lung bases, together with the onset of acute heart failure, (e) an early thready pulse with almost any form of arrhythmia, (f) rapid and often prolonged reduction in systolic pressure, (g) a diffuse, scarcely palpable cardiac impulse, (h) distant heart sounds and often a gallop rhythm, (i) a localized, evanescent pericardial friction rub, (j) short, mild fever with leukocytosis, (k) changes in the electrocardiogram which, as Wilkus (1940) emphasizes, only one with a thorough knowledge of the limitations as well as the advantages of this instrument can interpret, and (l) increased sedimentation rate. Coronary occlusion is often associated with or is the cause of abdominal signs and symptoms, and occasionally it will closely simulate an acute surgical condition of the abdomen. Also in instances in which there are not such typical cataclysmic attacks, the coronary origin of the symptoms may be easily overlooked in preoccupation with the patient's 'indigestion', but the history of prior events will often give an inkling of what is happening. Master *et al* (1941) found that in nearly half of their 260 patients premonitory symptoms had been experienced: fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, dizziness, angina. Occasionally occlusion may occur without any type of pain at all. It is to be hoped that the "inoxemia test" with which Levy *et al* (1941) are experimenting will be ultimately developed into a reliable diagnostic aid in doubtful cases.

TREATMENT OF THE ATTACK

Relief of Pain — Nitrites — In the anginal attack amyl nitrite by inhalation often brings relief in thirty seconds to one minute, it may be conveniently carried on the person in the form of a box of the 'penris,' one of which is crushed in the handkerchief for inhalation. But the odor is often objectionable to the patient and others who may be nearby when the necessity to use the drug arises, relief is also not so certain as with nitroglycerin. This latter drug may be prescribed as 1/100 grain (0.0006 Gm) hypodermic tablets, they are not volatile, do not deteriorate quickly, and are less expensive than amyl nitrite. The dose is 1 tablet, more or less, dissolved under the tongue, not swallowed, the full effect is more slowly achieved than with amyl nitrite—two to three minutes. While many patients have taken quite large doses of nitroglycerin with apparent impunity, a small number of pronounced reactions has been recorded: precipitate drop in blood pressure, severe headache and palpitation, and considerable discomfort for forty-eight hours. Sprague and White (1933) have observed such reactions only three times in their 900 patients, but they point out that it is an easy routine procedure in the office to try 1/400 to 1/200 grain (0.00015–0.0003 Gm) sublingually in each new case. Master (1935) believes these small doses to be routinely as effective as the larger ones. Christian advised some years ago that the patient be urged to remove the undissolved portion of the tablet as soon as relief is experienced.

Nitrites are contraindicated in the attack of coronary thrombosis because of the rapid fall in blood pressure which is a part of this syndrome.

Alcohol — A stout drink of whisky or brandy, or any hard liquor taken "neat" with very little water to 'chase' it, may bring quick relief in the anginal attack, this measure is said to be effective occasionally when the nitrites fail.

Opiates—In the attack of thrombosis it will be practically always necessary to give morphine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015–0.03 Gm), or dilaudid, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.00125–0.0025 Gm), at once. Larger doses are required to control this than any other pain—perhaps 1 grain of morphine in the first twelve hours, sometimes it is necessary to give it by vein. However, there are many careful clinicians who feel that it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of $\frac{1}{16}$ to $\frac{1}{8}$ grain (0.0002–0.0006 Gm), but it is perhaps best not repeated under several hours. When pain persists for several days, attempt is usually made to change to codeine in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015–0.03 Gm) every four hours.

Oxygen—In recent years Birch and Levy have been advocating the use of oxygen in cases of coronary thrombosis (for methods see Pneumonia). Many men testify to its ability to relieve dyspnea, cyanosis, restlessness, and pain. Boland (1940) makes the important point that in his experience such concentrations as are ordinarily reached in a tent do not suffice for complete relief but that this end is achieved by the employment of one of the newer types of inhalation apparatus which will deliver the higher concentrations—80 to 100 per cent—which he feels are necessary.

Other Measures—In 1 case of occlusion in which intractable pain did not yield to morphine in enormous dosage, Hirsch (1936) began the intravenous injection of 10 per cent evipal solution. After 1 cc the patient was drowsy, after 2 cc he was asleep, 4 cc were given in all. Sleep lasted fifteen minutes and on awaking there was only a dull precordial ache. In 2 cases in which morphine failed, Riesman stopped the pain at once by application of leeches to the precordium. Love (1937) found trichlorethylene inhalations helpful in a morphine resistant case, but Willus and Dry (1937) were disappointed in their results.

Stimulants—In occlusion, if there is peripheral circulatory failure, the most widely used drugs are metrazol, coramine and caffeine, I do not know that anyone has shown how much worth they really are.

Nursing Care—The simple uncomplicated anginal attack is an affair of moments only, is usually not seen by the physician, and requires no nursing care, but the patient experiencing thrombotic coronary occlusion is in an entirely different condition. Usually in a state of nervous if not actual circulatory shock when first seen, if at all feasible it is best to put him to bed at once wherever the attack has caught him, perhaps even without removal of clothes, for it is of the utmost importance to obtain quickly the maximum physical and emotional quiet with the minimum expenditure of either emotional or physical energy. The obtaining of competent nursing assistance and the relief of the suffering are affairs of first moment, removal to the hospital or to his own home of secondary importance. Then the siege must begin, a campaign whose sole object is to keep the patient *lying down* in bed for at least six weeks, to keep him quiet and unagitated during that time, and to cajole and induce him to like it. In the beginning he must not be permitted to move even enough to feed himself, and should be allowed to see as few people and attend to as few affairs as possible. The use of sedative drugs is not contraindicated (see Insomnia). Two or three months of enforced invalidism is an ordeal which few persons will accept without at least some show of

stubborn resistance, but if the patient does not know with certainty that such a period lies before him there will likely be much less struggle. Ricksman admirably says "The tactful physician will achieve his end by giving an answer which is true but not necessarily specific." Gradual propping in bed may begin a little before the sixth week, then in a few days more the feet may be allowed to hang over the side, and finally the patient may be got out by very slow stages so that he is walking about by the eighth week (the scar is thought to be firm now), perhaps slowly climbing stairs, if he must, in another month. I am merely condensing here the experience of many men in average cases, no time rules for these stages can be set, of course. The signposts that too much is being attempted: sensation of choking, return of pain or pressure, cyanosis, shortness of breath on exertion: this patient must be returned to bed.

Diet—For the first two or three days the patient is very unlikely to desire much food. Sipping of cold charged water or swallowing small bits of ice will usually control nausea, the addition of bismuth subcarbonate and sodium bicarbonate, each in 15 grain (1 Gm.) doses will almost certainly do so, unfortunately, however, the nausea and possibly vomiting induced by morphine are not easily controlled by any means that I know—the employment of benzedrine sulfate for this purpose, successfully reported by Guyot (1941), seems to me a very radical procedure, but perhaps others will confirm his finding that it was very helpful and apparently not in itself harmful. Dry toast, chicken butter-milk, apple sauce, strained vegetables, tea or coffee may all be added gradually and in small quantities. Throughout the bed-ridden period the food intake must be kept small. Master and his associates perhaps ritualize the thing more than most others and actually keep their diets lower, but they also describe good results. For at least three and preferably four weeks they limit fluids to 1000 or 1200 cc. and calories to 800, the following is a sample diet containing 100 Gm. carbohydrates, 50 Gm. proteins, 20 Gm. fat, with adequate vitamins and calcium. They claim as much reduction in basal metabolic rate with this regimen as is accomplished by thyroidectomy and that patients feel so well under it that persuasion is often required to get them to increase their food intake.

800 CALORIE DIET (MASTER, JAFFE AND DACK, 1936)

<i>Breakfast</i>	<i>Sample Menu</i>
100 Gm. 12 per cent fruit	$\frac{1}{2}$ medium orange
10 Gm. cereal	2 tablespoons cooked cereal
200 cc. skimmed milk	1 cup
1 egg	1 egg
15 Gm. bread	$\frac{1}{2}$ slice
<i>Dinner</i>	
60 Gm. meat	2 ounces meat
100 Gm. 3 per cent vegetable	$\frac{1}{2}$ cup spinach
100 Gm. 12 per cent fruit	3 plums
15 Gm. bread	$\frac{1}{2}$ slice
200 cc. skimmed milk	1 cup
<i>Supper</i>	
1 egg	1 egg
100 Gm. 3 per cent vegetable	$\frac{1}{2}$ cup canned string beans
100 Gm. 12 per cent fruit	1 medium peach
15 Gm. bread	$\frac{1}{2}$ slice
200 cc. skimmed milk	1 cup

Care of the Bowels—Unnal and bed pan will of course be used throughout the entire time. Straining had best be avoided by the use of liquid petrolatum. It is best to permit the costiveness induced by the opiates in the beginning to persist for several days, which can easily be done as the patient is taking practically no food, a larger dose of cathartic than is usual will then be required to obtain the first movement.

SUBSEQUENT TREATMENT

Only during the attack can one distinguish therapeutically between angina pectoris and thrombotic occlusion. Subsequently, the sole purpose of treatment is to prevent another attack—to prevent another attack of angina not only because the experience is terrifying and painful but because instead of angina it may be occlusion which suddenly presents, to prevent another attack of occlusion because the next one may be the last.

Mode of Life—If the overworked, overworried, overwrought individual with coronary disease can be brought to relinquish in whole or in large part his professional or business affairs, and can be brought to adopt the mode of life of a person of indolent habit and independent means, and to model his temperament upon that of the cow, and can be induced to journey south in a leisurely fashion during the inclement months, going preferably to a spa, and can be reeducated to eat slowly of light foods in small amounts—that is to say, if all that is practically impossible for the average competing individual in a work-a-day world can be accomplished, then the patient may be said to have the best chance of prolonging his life beyond the four or five years allotted most of his fellow sufferers. I do not know of any well substantiated evidence that altitudes of 10,000 or 12,000 feet, which is about the average ceiling of transport planes in this country, is harmful, though it is commonly said that these individuals should avoid such altitudes. Palmer's (1937) studies indicate that the probability of a patient being able to lead a fairly active life following recovery from an attack of thrombosis is almost twice as great if his heart is normal in size as if it is enlarged. It is probable that the height of the blood pressure is of little significance. Many physicians do not permit sexual intercourse, it seems to me that in a certain sort of individual the loss of this right might in itself provoke an attack. At any rate, Master and Dack's (1940) study of a very large number of patients, both private and clinic and of all classes and types of occupation, clearly indicates that an attack of acute coronary occlusion in itself need not be looked upon today, as it was a few years ago, as invariably constituting sufficient reason for permanent disability, complete recovery and full or partial economic restitution are of common occurrence. This group of observers is also championing the position that physical exertion bears no causal relationship to coronary occlusion. Drake (1940) has reported the record in longevity, I believe, a man who returned to his usual occupation after suffering a myocardial infarction at the age of forty, at sixty seven he developed angina, at seventy five another attack of coronary thrombosis which did not seem to change his physical condition after healing had taken place, at seventy-eight a third coronary thrombosis from which he recovered after many weeks, and sudden death in a nocturnal attack of angina at the age of eighty.

Diet—Gilbert (1936) writes 'The diet should be adapted to the needs of the individual patient. It should be such as to be readily digestible and

one which cannot cause gas. Full heavy meals are to be avoided. Articles of food not well borne must be discovered by the individual patient, indeed having reached the age of most of these patients he has long known the things which disagree with him and needs only to eliminate these from his diet. Levy (1937) has shown that coffee will induce cardiac pain in some individuals. Hydrochloric acid with meals is helpful in some patients, carminatives after meals are not contraindicated.

There are indications that obesity is a handicap, more than half Goldsmith and Willius' (1937) series of 300 patients at the Mayo Clinic were overweight. However, in reducing the weight of the victim of coronary disease, thyroid extract should definitely not be used.

Tobacco and Alcohol—It seems to me that there has been considerable misunderstanding of the report of White and Sharber (1934), who compared the past alcohol and tobacco habits of 760 angina pectoris patients with 760 individuals who did not have angina. They found no evidence that the use of either of these drugs of addiction played an important role in the genesis of the malady, but they also stated that in occasional cases the use of tobacco apparently aggravated or precipitated attacks and indulgence in alcohol helped to prevent or to relieve them. Many doctors are overlooking the latter part of this evidence in their joy at finding that they can continue to smoke without endangering their coronaries—perhaps it would have been better to use the word 'surprise' instead of 'joy' above, for most of us really suspected the habit to be dangerous. The evidence from Willius' section on cardiology at the Mayo Clinic, published by English *et al.* (1940), while not conclusive certainly points toward smoking as a possibly contributory factor, especially in the younger age groups. May I say that when or if I come down with coronary disease I shall stop smoking if I can and at once change my drink from beer, which distends the stomach to hard liquor?

Sedatives—Certainly many of these individuals will profit at times from the judicious use of sedatives and hypnotics, see the article on Insomnia.

Xanthine Vasodilators—Many physicians have thought these drugs helpful, though most patients are somewhat upset by them, the untoward effects are nausea and sometimes vomiting, a burning pain in the epigastrium or under the sternum, palpitation, dizziness, headache, 'nervousness,' and a few other minor complaints. The drugs of the group and their dosage follow, they are given in capsule or tablet form three or four times daily, best during instead of before or after meals, enteric-coated tablets, now available are said to lessen the incidence and severity of unpleasant symptoms.

Theobromine	5 to 7½ grains	(0.3-0.5 Gm.)
Theobromine sodium acetate (agurin)	10	(0.6 Gm.)
Theobromine sodium salicylate (d uretin)	10	(0.6 Gm.)
Theobromine calcium salicylate (theocalcin)	7½ to 10	(0.5-0.6 Gm.)
Theophylline (theocin)	1½ to 3	(0.1-0.2 Gm.)
Theophylline sodium acetate (theocin soluble)	2½ to 5	(0.15-0.3 Gm.)
Theophylline calcium salicylate (phyllcin)	4	(0.25 Gm.)
Theophylline ethylenediamine (aminophyllin)	1½ to 3	(0.1-0.2 Gm.)

Not only tolerance but also cross tolerance to these drugs seem to be acquired by an occasional patient, some men have the medication taken for four consecutive days of each week and omitted on three, and they alternate a theobromine with a theophylline preparation. Gilbert (1934), for example,

begins with theocalcin—confirming the earlier observation of Gilbert and Kerr (1929) that this drug rarely causes distress—and alternates with aminophyllin and phyllicin and the others of the group as seems desirable. Smith *et al* (1935) feel that their clinical experience confirms the experimental evidence of the superiority of theophylline to theobromine; they use only theophylline itself and aminophyllin. Coogan (1934) was pleased with his results in ambulatory patients of the dispensary type using phyllicin only. In 18 physician patients who did not know which of the xanthines they were taking, Hyman (1934) found most satisfaction with diuretin. Brown and Riseman (1937) obtained the best effect in their patients with agurin and theocin soluble. The studies of Levy *et al* (1940) pointed strongly toward the ability of aminophyllin to postpone the appearance of pain. McMahon and Nussbaum (1940) concluded that favorable changes in the electrocardiogram often result from the intravenous administration of this drug.

So much for the evidence favoring the use of xanthines in coronary disease—indications of their presumed value but also considerable disagreement regarding the preferred preparation. Unfortunately there is a reverse to the coin for in two carefully controlled studies, those of Evans and Hoyle (1933) in England and Gold *et al* (1937), in the United States, there was failure to adduce any proof that these drugs are actually of value in this disease. In the latter studies, 200 courses of treatment with xanthines in 100 patients were alternated with courses of placebos or some other agents; the patients could detect no differences. Christman (1937) expresses himself unconvinced of the effectiveness of these drugs. However, LeRoy (1941) has recently given aminophyllin or placebos to 68 patients over a period of two years. He says that aminophyllin benefited about 75 per cent of the patients, placebos and sedative drugs about 20 per cent—so the subject is wide open again!

Nitrites—The disagreeable effects of drugs of this group, occasionally seen when amyl nitrite or nitroglycerin is used for the relief of an attack of angina, are much more frequent accompaniments of the routine use of the longer acting members, the tetranitrites and sodium nitrite. But in an individual who is having many anginal attacks during the twenty-four hours it is sometimes possible to lessen both their number and severity for a time at least by the use of these preparations; the result is said to be especially gratifying in those whose nocturnal attacks make the nights very miserable. Erythrol tetranitrate and the "diluted erythritol tetranitrate" of the U.S.P. are available in $\frac{1}{4}$ and $\frac{1}{2}$ grain (0.015 and 0.03 Gm.) tablets; the dose is $\frac{1}{2}$ to 1 grain every four to six hours; maonitrl hexanitrate may also be used in the same dosage. These salts are all rather expensive. Sodium nitrite is cheaper but very irritating to the stomach. Many practitioners who formerly used the latter drug thought it more effective when combined with sodium or potassium iodide. The sodium nitrite dose is 1 to 3 grains (0.06–0.2 Gm.) in tablets or capsules. I believe an enteric-coated tablet is now also available which should cause less gastric disturbance.

Cobra Venom—Parsonnet and Bernstein (1940) were pleased with the results of cobra venom therapy in 5 otherwise intractable cases. 5 mouse units intramuscularly repeated on the following two days, then tapering off every other day, finally twice a week. This agent is very slow in producing its effects and is therefore not at all suited to the control of pain in the acute attack.

Codeine—Sproull (1936) says that in the elderly, thin, arteriosclerotic individual, still actively hustling about in life despite his enlarged heart and anginal symptoms, codeine sulfate is very valuable. He begins with $\frac{1}{2}$ grain (0.008 Gm) four times daily and after about ten days reduces the dose as much as possible.

Dextrose and Insulin—Smith (1933), in England, reported 6 severe cases in which he used glucose (dextrose) and insulin for periods varying from two to seventeen weeks, 5 units of insulin before breakfast and before the evening meal, each dose being followed by 30 Gm of glucose taken with the meal. All conditions as to work, rest and medication were maintained during the study just as before it began. In all instances the relief obtained after being on the treatment for a while was almost complete and when the pain returned after the conclusion of the study it was again overcome by return to the glucose-insulin therapy. Smith feels that anginal pain is related to faulty carbohydrate metabolism in the heart and that insulin acts immediately through its stimulating effect upon glycogen metabolism in the organ and progressively by promotion of the combustion of fat thus leading to the early resolution of atheromatous changes in the coronary arteries. It has been pointed out earlier that many observers look upon the use of insulin in coronary disease as very dangerous and try to treat diabetes without the drug when it is complicated by grave cardiac disturbances. It is not unlikely that Smith was much reviled. However, in the United States Nichol of Miami was able to report improvement in half of his 20 cases; he used 15 to 30 units of insulin daily with extra feedings of 30 Gm of glucose in fruit juice two hours after each meal. In the discussion which followed the reading of Nichol's paper, Hyman of New York, who with Parsonnet coined the phrase "postinsulin angina" some years ago, expressed himself as unalterably opposed to the use of insulin in average instances of coronary disease, but thought that it might be admissible in certain groups of cases. The danger that some sort of superclassification of coronary cases is impending is brought out in discussions of this sort.

Digitalis and Quinidine—I think that upon the whole the profession is fearful of the use of digitalis in coronary occlusion in the belief that it may (a) rupture the infarct through increasing the force of the heart's contraction, (b) predispose the heart to ventricular tachycardia, (c) constrict the coronary vessels. But such an authority as Gold (1939), who has gone into this matter extensively, is certain that there are no grounds for any of these fears. He feels that the indications for digitalis in coronary occlusion are precisely those that would obtain otherwise; i.e., the drug should be used if there supervenes an auricular fibrillation or a right or left ventricular failure. Such disturbances occur very rarely during the early days of a coronary episode and not always by any means at a later period or during the subsequent attacks, therefore there can be no thought or excuse for routine digitalization of these patients. When the drug is indicated and employed Gold would not have it used in a hectic fashion—allow a somewhat longer time than usual for the accomplishment of full effect.

Ventricular tachycardia being an arrhythmia much feared after coronary occlusion, there has arisen some interest, probably initiated by Levine (1936) in the "prophylactic" use of quinidine to prevent this occurrence, ventricular tachycardia going over into fibrillation of course means death. Borg (1939) employing quinidine sulfate 3 grains (0.2 Gm) three times daily in a large

group of clinic patients of the sort in whom sudden death was to be expected felt that the drug probably lessened the incidence of such deaths. Woods and Barnes (1941), at the Mayo Clinic, seem convinced that it is rational and probably important to give the drug to any patient who has had an occlusion, particularly if the patient is experiencing frequent premature ventricular contractions. But Gold (1939) is apparently unconvinced that this "prophylactic" treatment has merit.

Surgical Measures—*Cervical sympathectomy* This operation has been practically abandoned, though I believe a few surgeons continue to perform it in patients under forty five years of age. Raney (1939) has recently described a 'preganglionic' resection, but I have seen no reports of anyone else performing this operation. *Paravertebral alcohol block* This procedure has fared somewhat better. Levy and Moore (1941) report relief in 77.5 per cent of 40 patients, the relief being marked and permanent (8 cases followed more than six and 2 cases more than nine years) in 47.5 per cent. In 5 cases pleural effusion developed on the left side but was absorbed without aspiration within a week. Most of the patients suffered from painful intercostal neuritis which lasted from a few weeks to several months. *Grafting operations* Claude Beck (1937) has been attempting to increase the blood supply to the myocardium by grafting tissues upon the heart, an experimental procedure in hopeless cases which has at least the merit of supreme audacity, others, both in England and America, have reported satisfactory results from this operation. *Total thyroidectomy* There does not any longer seem to be much interest in this matter.

Roentgen Therapy—Raah (1940) has attempted to relieve the symptoms of angina pectoris by restricting the acute discharges of adrenalin through roentgen irradiation of the suprarenal glands. Success was claimed in 76 of 100 cases. This is a new and radical type of treatment and of course the results will need independent confirmation before one can consider them valid, furthermore the control of such an experiment would be difficult in the extreme.

AORTITIS AND ANEURYSM

(See under the *Treatment of Cardiovascular Syphilis*)

THROMBOANGITIS OBLITERANS

(*Buerger's Disease*)

This peculiar disease, first described by Buerger, in 1908, is an inflammatory affection of the deep seated arteries and veins and the superficial veins of the lower extremities occasionally of the upper extremities. It occurs principally in middle aged males though women, in whom it seems to be a

milder affection, are also very occasionally afflicted. We nowadays do not look upon this as almost exclusively an affliction of Jews, of Horton's (1938) 927 cases, 670 were in Gentiles. The etiology of the disease is unknown, but it is generally conceded that excessive smoking plays some part, there are now available several studies showing that peripheral vascular constriction accompanies the act of smoking. The studies of Theis and Freeland (1941) suggest that a disturbance in the utilization of oxygen, consequent upon constriction of vessels, is one of the conditions underlying the pathology of the disease. Sulzberger and Harkavy independently arrived at the belief that there may be an allergic hypersensitiveness to tobacco underlying many of the cases, Westcott and Wright, however, do not share this opinion. Kaunitz' interesting thesis that Buerger's disease and related vasomotor and trophic disturbances are the present-day expression of ergotism, gains support from Klein's (1937) showing that our common cereals are frequently fungus infested. McGrath's (1935) animal studies suggested to him the possibility that the female rarely develops the disease because of the protective action of the estrogenic ovarian substance. Rahinowitz (1938) looks upon impaired phospholipin metabolism as responsible for all findings. Goodman (1941) is very interestingly contending that thromboangitis obliterans is a late manifestation of typhus fever. The character of the lesion suggests either a toxic or bacterial exciting factor, there is acute inflammation with occlusive thrombosis, organization or healing canalization of the clot, disappearance of the inflammatory products, and the development of fibrotic tissue that binds together the artery, vein and nerves. The cardinal signs and symptoms of the disease which usually develops insidiously, are severe constant pain in the calf and foot and also intermittent pain of the claudication type, pallor of the limb when it is raised above the horizontal position and great redness (rubor) when it is dependent, coldness of the extremity, and lack of pulsation in the arteries affected. Migrating phlebitis of the superficial veins is of frequent occurrence. Ultimately, ulceration and gangrene occur in the great majority of cases.

Cohen and Barron's (1936) review of the autopsy literature reveals thromboangitis obliterans as probably a generalized disease process which may affect vessels anywhere in the body. Hausner and Allen's (1940) observations at the Mayo Clinic substantiate this viewpoint. 57 per cent of 500 patients had coronary involvement, 2 per cent cerebrovascular involvement, and there were three cases of abdominal and one of pulmonary involvement.

THERAPY

This disease being of unknown etiology, of serious import, and as yet without a specific remedy, it is to be expected that a large number of remedial agents and measures shall have been tried. I shall discuss here only those that seem to be holding their own as therapeutic procedures, but in attempting to evaluate them the reader should give full consideration to the following statements of Perla (1925). 'Thromboangitis obliterans is an extremely chronic disease, often lasting as long as fifteen or twenty years. More than 80 per cent of all cases give a history of remissions during which the patient is free from all symptoms. These remissions occur spontaneously at almost any stage of the disease and last from a few months to several years, fre-

quently as long as five ten and even fifteen years Temporary arrests have been reported as cures following almost every new therapeutic innovation In this disease particularly a temporary arrest of one year is not evidence of more than a remission In Horton's (1938) review of 948 cases at the Mayo Clinic it was revealed that approximately 30 per cent of patients require an amputation within three years of onset of the disease 40 per cent within five years and 60 per cent within ten years

General Routine—Rest in bed for a month or more is imperatively necessary in every case no matter to what stage it is first seen and when improvement takes place the return to partial activity should be extremely gradual The patient should wear ample underclothing and socks in winter and perhaps even woolen stockings up over the knees fleece lined shoes when outdoors and loose woolen socks in bed add greatly to the comfort of many individuals Heat to promote collateral circulation is employed either by means of the electric pad or the electric bulb cradle or by any other means through which heat at or slightly below the temperature of the body may be applied to the affected extremity continuously for a long period of time Overheating will only increase the pain and is extremely likely to initiate the breakdown of the tissues as indeed is any other type of trauma, these patients should take even greater care of the feet than diabetics if such a thing is possible At the Post Graduate Hospital in New York Wright (1940) and his associates have given up the use of contrast baths and also wet dressings but they employ sitz baths at about 100° F (37.8° C) for fifteen to thirty minutes once or more each day if there is no open lesion and soaking of the limb with an open lesion in boric acid solution or physiologic saline solution at the same temperature A warm cradle is employed to prevent chilling after these treatments Wright is absolutely opposed to the use of heat lamps diathermy or short wave machines

Smoking—All authoritative students of this disease are in agreement that tobacco must be absolutely interdicted witness the following statements Horton (1940) We at the Clinic are of the firm conviction that all patients who have thromboangitis obliterans should stop smoking Allen (1939)

Hardly new but well worth emphasizing again is the importance of complete cessation of smoking Wright (1940) Good results are to be expected from the general treatment outlined here provided the patient will completely stop smoking

Alcohol—In contrast to tobacco alcohol is definitely a dilator of the peripheral vessels All observers use it freely in treatment of this disease often proceeding to the point of keeping the patient mildly inebriated during a critical period such as when gangrene is impending Wright (1940) says that unless there is a definite contraindication—severe diabetes gastric ulcer—all patients with this disease should have some alcoholic beverage each day for the remainder of their lives DeTokats *et al* (1939) while not denying the salutary circulatory effect of alcohol deplore the fact that these patients not infrequently become habitual drunkards

Miscellaneous Drugs—Five to 15 grains (0.3–1 Gm) of *potassium iodide* is given twice or thrice a day during the whole period of treatment by many physicians, but it is doubtful whether structural changes in the vessel walls reduction of the viscosity of the blood or hastened absorption of these nonspecific cellular exudates actually follow upon its use I am convinced that

the various *tissue extracts* are still in the experimental stage, and none too promising either, for the results do not seem to be striking in any of the specialized clinics in which these studies are being pursued. There have been reports of the effective use of all the following agents, but a detailed description of the methods does not seem warranted in the case of any of them: *mecholyl*, *prostigmin*, *popaverine*, *nitrites*, *xanthines*, *testosterone*, and of course *thiamine* (vitamin B₁).

Passive Vascular Exercise (Buerger Method)—The original description is still the model. The affected limb is elevated, with the patient lying in bed, to from 60 to 90 degrees above the horizontal, being allowed to rest upon a support for from thirty seconds to three minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about three to five minutes during which time an electric heating pad or a hot water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes. These cycles are repeated over a period of about one hour, some 6 to 7 cycles constituting a *séance*.

The number of *séances* per day varies for individual patients.

Passive Vascular Exercise (Oscillating Bed Method)—In a few hospitals there are special beds in which in effect the Buerger exercises can be performed without any active participation on the part of the patient—the bed does the whole thing except pay the costs, which unfortunately limits the usefulness of the whole business.

Passive Vascular Exercise (Machine Method)—Landis and Gibbon (1933), and Herrmann and Reid (1933), independently devised apparatus for the treatment of chronic occlusive arterial disease through promoting peripheral blood flow by alternate suction and pressure applied to the affected extremity. The method has had enthusiastic trial, but the results in Buerger's disease have not been good in the hands of groups other than the originators. Wright (1940) has given it up entirely, and DeTakats *et al* (1939) so thoroughly qualify the indications for its use that I am unable to state them clearly here except to say that the class of patient who profited most in their experience was the one still a little affected by the disease that he was unlikely to present himself for treatment. The apparatus is noisy and often causes the patient much discomfort.

Intermittent Venous Hyperemia—Collens and Wilensky (1936) apply a pneumatic cuff to the proximal portion of the affected extremity and create alternating periods of venous congestion and release. They have described excellent results in a large number of cases in recent years. Kramer (1939) reported good results in 6 of 21 patients. Wright (1940) and associates have given the method a thorough trial and then given it up. DeTakats *et al* (1939) seem still to be experimenting with it.

Sodium Chloride Intravenously—The intravenous injection of 5 per cent aqueous solution of sodium chloride, introduced by Silbert in 1923, is the only one of the salt injection types of treatment that has held its own.

against all the other methods of treatment. The solution is prepared in freshly distilled water filtered and sterilized at once. The initial injection is 150 cc. all subsequent ones 300 cc. taking about ten minutes for completion. The patients remain ambulatory and can get up at once after each injection; there are no reactions if the solution is properly prepared though during injection the patient frequently feels very warm and thirsty. Injections are at first given thrice weekly, then twice, then at increasing intervals as improvement occurs. Duration of treatment—disappearance of symptoms or maximum possible improvement—is from six weeks to two years. In 1935 Silbert reported that he had treated 524 patients by this injection method with improvement in 83 per cent of the cases and amputation in only 7.6 per cent, among whom about half had persisted in smoking against advice. Wright (1940) seems to consider this the treatment of second choice, typhoid vaccine being the first (see below).

Foreign Protein Fever Therapy—Any of the fever producing methods (see *Neurosyphilis*) are employed but principally typhoid vaccine. Wright (1940) aims at obtaining a rise in oral or rectal temperature of 2° or 3° F (1° or 2° C) without a chill. His first dose is 5 000 000 organisms and injections are given every three days provided that the effect of the preceding one has completely worn off. Increases of 3 000 000 to 5 000 000 organisms are made whenever the reactions are not satisfactory, decreasing by the same amounts if the temperature has exceeded 103° F (39.5° C) and a chill has occurred, with most patients the top level at which treatments have continued for long periods has been between 70 000 000 and 130 000 000 organisms. Treatments are suspended during acute infections or other serious illnesses. Wright does not nowadays employ stock typhoid vaccine but rather one which is specially prepared for him and which he believes permits of more accurate measurement of dosage. Allen (1930) of the Mayo Clinic like Wright considers this the best of all treatments in many cases.

Peripheral Nerve Block—For relief of pain the peripheral nerves are blocked by alcohol injection, crushing or section with immediate suturing. This is in no way a specific treatment and is employed only as a palliative measure, but it is said to obliterate pain completely in nearly all instances; it does not relieve intermittent claudication. By the time regeneration occurs in about a year, arrest of the disease will have taken place if the other elements of treatment have been successfully applied. Walking is not interfered with by these operations (which are simply performed) but the wound surfaces become anesthetic and can therefore be painlessly cleaned and dressed. De Takats *et al.* (1939) have finally dropped the crushing operation because of many anatomic variations, very painful paresthesias during the period of returning sensation, and the loss of defensive reactions in the denervated areas. Perlow and Halpern (1939) now prefer peripheral nerve injection with procaine in oil.

Sympathetic Ganglionectomy—Adson and Brown (1932, 1936) found that quite considerable improvement resulted from the performance of sympathetic ganglionectomy in 83 per cent of their 104 patients (100 patients plus 4 who had both upper and lower extremity involvements). My impression is that most surgeons of experience in the disease do not believe that such results are obtainable in the ordinary run of cases, that is to say that perhaps a preponderance of relatively early cases is seen at the Mayo Clinic. However

Smithwick (1940) obtained "excellent" results in 22 instances in 52 operations on 30 patients and "improvement" in 27 other instances. DeTakats *et al* (1939) claim success in 49 instances in 56 operations on 21 patients, but their criteria of suitability for operation are the following: absence of acute inflammatory stage, below forty years and with definite collateral reserve, poor response to conservative therapy. Horton, reporting the Mayo Clinic statistics in 1938, shows that of the 193 patients given sympathectomy, 26 per cent later underwent amputation. He says "It is well recognized that sympathectomy does not cure thromboangitis obliterans. Probably it does not even alter the course of the disease in the blood vessels. It does, however, bring about the maximal blood flow to the sympathectomized extremities and for that reason is still the most logical surgical procedure in properly selected cases for increasing the blood supply." The operation is a formidable affair for both surgeon and patient and seems to be attended by a mortality of about 4 per cent in the best of hands.

VARICOSE VEINS

Varicose veins of the legs develop principally in women in the early childbearing years, but in some instances they make their appearance at adolescence or at the menopause. The incidence is much lower in men. The varicosities are usually only on the inner aspect of the calf and thigh and the inner and posterior aspects of the knee, but in advanced cases they are present on the posterior and outer aspects of the limb also. The veins appear as tortuous bluish cords beneath skin that is often atrophic, shiny and pigmented, sometimes there is associated secondary telangiectasia (dilatation of capillaries). Some patients present doughy induration of the ankles. Lymphedema, erythema and eczema are common, but the most serious complications are phlebitis and the sluggish chronic varicose ulcer which appears on the lower third and usually inner aspect of the leg and tends to attain very great size. This ulcer is accompanied by marked inflammation and tenderness and has sloping edges and a coarse granular exudate, in contradistinction to the luetic ulcer with its punched-out edges and serous exudate, and the tuberculous ulcer with undermined edges and a grayish necrotic exudate covering the base. The subjective symptoms of varicose veins are a feeling of weight in the legs and dull aching pain, which is much relieved when the patient lies down or elevates the legs on a chair. Spontaneous disappearance of the varicosities does not take place. There seems to be an hereditary tendency toward development of the disease, but its real cause remains unknown.

THERAPY

Walking exercise favors venous return but standing is very bad for these patients. Great care should be taken to avoid even the slightest injuries to the legs as trauma favors the development of ulcer, but unfortunately just the class most often afflicted with varicosities, *i.e.*, the laboring class, can least afford to heed this admonition seriously. The wearing of elastic stockings,

or the employment of the woven elastic bandage of the ace type, brings considerable relief to many individuals. Tight garters and girdles should not be worn. The legs should be elevated during every moment that it is not absolutely necessary for the patient to be standing. The reduction of obesity is probably of advantage.

CHOICE OF PATIENTS FOR INJECTION TREATMENT

The venous system of the lower limb is divisible into 3 parts (a) the deeply situated femoral and popliteal veins and their tributaries (b) the superficial internal saphenous vein and its tributaries serving the front and inner aspect of the leg and thigh and joining the femoral in the foramen ovale, and the short saphenous vein coursing superficially on the back of the leg to join the popliteal vein at the upper border of the popliteal fossa and (c) the communicating systems of veins between the deep and superficial systems. Now since the substances used for injection of varicose veins provoke injury and adhesion of the vessel walls, i.e., occlude the vessels, it is obviously of greatest importance to determine if the deep venous system is intact and functioning well before any part of the superficial system is destroyed. The method by which presence of full patency in the deep system is determined is called 'Perthes test'—obliterate the superficial system with a blood pressure cuff over the foramen ovale and have the leg exercised, deep patency is indicated by emptying of the varices and absence of subjective symptoms. Obstruction by dilatation of varices and pain (Swinton sends the patient around the block with an ace bandage obliterating the superficial circulation, if she comes back with the bandage in her hand he considers the deep circulation not competent.) Injection treatment is not to be given individuals whose deep venous circulation is impaired. In addition the following seem to be definite contraindications within the limits specified: (1) active or recently subsided phlebitis (2) any condition causing the patient to be bedridden (3) saline solutions should not be used in nephritics and sugar solutions not in diabetics otherwise weighing each case with judgment such patients may be injected (4) in cardiac decompensation injection is usually contraindicated but Swinton points out that mild cases are sometimes helped—Horslick (1935) says that the multiple injection method should not be used in such people because it is too tiring (5) advanced age in itself is not a contraindication nor is peripheral arterial disease apparently, but in the latter cases the arterial rather than the venous disease usually demands preferential treatment (6) the dictum that injections should not be made during pregnancy was first challenged by McPheeters and more recently by Cheatnam and Peck, and by Nicholas. Swinton does not consider it an absolute contraindication, even to the injection of vulvar varices. Edwards also injects such varices, which frequently cause much annoyance and may rupture during delivery, but he admits that after term the engorged veins of the lower extremities and vulva may greatly diminish in size. Quinine solutions are not to be used during pregnancy, of course, (7) infectious processes anywhere in the body, even the common cold contraindicate the treatments by common consent, but some men go so far as to include such a large list of focal infections as would practically eliminate three fourths of the candidates. I should think (8) neurotics stand these treatments like everything else very poorly. (9) D. Abreu found evidence of thrombosis of the inferior vena cava in 2

patients who told him nothing about the tortuous veins on their abdomens—to avoid the disaster which would probably attend injection in the lower limbs in such cases he advises routine scrutinizing of the abdomen in all patients

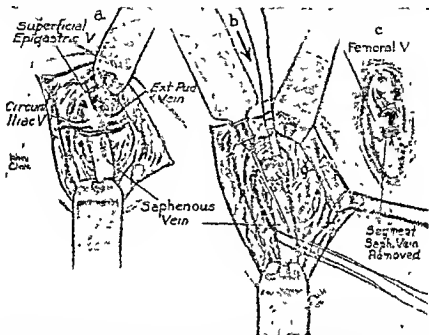
LIGATION PRELIMINARY TO INJECTION

Despite the enthusiasm for injection to the exclusion of all other methods of treatment, which has gripped the profession since about 1920 admission is being forced that recurrences are encountered with embarrassing frequency. Reexamination of the anatomic and physiologic bases on which the treatment rests indicates that the fault usually lies in the existence of incompetent valves in the internal saphenous system allowing a reversed flow of blood from the saphenofemoral junction such downward coursing blood will recanalize the sclerosed varix and dilate a collateral or redilate a varix below. Recognition of this fact is causing many conservative men to turn back to preliminary ligation of the internal saphenous vein at the saphenofemoral junction in selected cases the basis of selection being a positive Trendelenburg test lay the patient flat elevate the leg and assist emptying of the varices by gently stroking toward the foramen ovale then make pressure with the finger on the foramen and stand the patient up quickly the varices will begin to refill slowly from below, but when the finger is released filling takes place rapidly with blood which is seen to shoot downward from above.

The technic of preliminary ligation and massive retrograde injection of the upper saphenous system as practiced at the Lahey Clinic of Boston is described as follows by Swinton (1936) who has kindly permitted me to use his illustration

The patients are admitted to the hospital the night before operation the groin carefully prepared as for any surgical operation and usually the entire perineum shaved. In many of the very obese patients it may be safest to continue this preparation for one to two days until the area is clean. Many of these cases are done under local anesthesia yet we prefer in the good risk patients to use cyclopropane as there is less distortion of the tissues and less discomfort to the patient. A transverse incision is made parallel to Poupart's ligament about 1 cm below it continued medially from the femoral artery which can always be palpated. The saphenous vein will be found immediately beneath the superficial fascia. The dissection of the saphenous vein is then carried up into the junction with the femoral and all the tributary veins in that area are exposed. These high branches must be ligated if the procedure is to be successful and emphasis is to be laid on this careful high dissection. The superficial epigastric vein the superficial iliac circumflex and the superficial external pudendal are quite constant empty into the internal saphenous within the last 3 cm of its course and must be ligated with the main trunk of the internal saphenous if all back pressure is to be eliminated and the setting up of a collateral circulation in that region avoided. After the veins have all been carefully identified the tributaries are divided. The main trunk of the saphenous is then ligated $\frac{1}{2}$ to 1 cm from the femoral but not divided. At this point we perform a retrograde injection of the entire system with one of the milder sclerosing solutions. We believe this is also a distinct advance in the injection treatment. Varices in the thigh are frequently difficult to locate because of fat the thigh in many women is very sensitive and we find that following the retrograde injection further injections into the thigh are

seldom necessary. We employ a solution of 10 per cent saline combined with 30 per cent glucose for this massive injection. The amount required is variable but ordinarily 10 to 20 cc. is sufficient to obliterate all the veins down to the knee. We have used 40 cc. and thrombosed the entire saphenous system down to the ankle but we do not believe this is a safe amount. Following the retrograde injection a second ligature is placed on the saphenous 1 to 2 cm. below the first and the intervening section of vein removed. We feel that it is somewhat dangerous to divide the vein before completing the dissection as these vein walls are frequently very thin and slight traction on such a stump could very easily tear into the femoral itself. Ace bandages are then placed about the leg at least to the knee. The patients are discharged from the hospital the following day and usually return to work after a total disability of two to four



Method of performing a retrograde injection of a sclerosing solution into the internal saphenous system at the time of the ligation of the saphenous vein. Note that all branches and the internal saphenous vein itself have been ligated before the injection is done (Swinton, N. W. Surg. Clin. N. A., 16, 1723, 1936, by permission of author)

days. Following operation the patients are urged to take a few steps each hour. After a general anesthetic this may be delayed a few hours but all patients have taken a few steps by the evening of the operation. Subsequent injections can be done at the convenience of the patient. . . . They may be started as soon as the patient is discharged from the hospital. There is probably slightly less discomfort if they are delayed a week following the operation. We have found that smaller amounts of the solution are advisable following preliminary ligation at each treatment than we used formerly when the vein had not been previously ligated. . . . Many fewer injections are required where the vein has been ligated previously and most cases can be cleared up in 3 to 6 visits that formerly took two to three times that many injections. A word of caution should be said about discharging these patients. We ask

these patients to return for examination and tell them that 1 to 2 further injections may be necessary one month after the completion of the first series of injections, then three months later and again at the end of one year. Only in this way do we feel that all the varices will be found and obliterated."

I think the fact should be stated here that at least two men of vast experience in the injection of varicose veins Isaak (1940) and Hayes (1941), have expressed the opinion in no uncertain terms that the mortality is much higher following ligation and retrograde injection than following injection alone. If this is true the general practitioner is in the safer camp for most of the ligations are still done by surgeons or specialists in peripheral vascular clinics.

CHOICE OF SCLEROSING SOLUTION

Of all the large number of competing agents I shall include here only those few with which most experience has been had. *Sodium morrhuate* has apparently most nearly filled the ideal requirements and has supplanted all other agents in a large majority of clinic and private practices. It is used in 5 per cent solution in a quantity of 0.3 to rarely more than 3 cc. at any one site (in using the multiple injection method—see below—Horlick finds a total of 10 cc. in 0.25- to 0.5-cc. individual doses, suitable in average cases). It causes very little pain on injection and severe and lasting after pain in only an occasional patient. Sloughs are rarely reported as a result of injection outside the vein, and such as occur do not seem to be so serious as those caused by quinine and salicylate. Occasionally the injection causes a reaction with thickening, tenderness and discoloration around the veins; this reaction extending as it does for some distance along the course of the vein is very alarming but it usually subsides in a few days. Cooper (1934) says it presages an excellent result, but I doubt if all observers are convinced of this. Further dermatitic and urticarial rashes of a nature very suggestive of allergic reactions have been reported, as also severe general shocklike states and 1 case of very alarming bradycardia. But none of these systemic reactions is seen with great frequency. The new chemical monoethanolamine oleate, proposed as a substitute for sodium morrhuate by Meyer (1938), already has one allergic type of death chalked up against it, but it is only fair to say that Golden and Heyerdale (1940) have stated their belief that the number of severe reactions and even deaths due to sodium morrhuate is considerably greater than the record indicates. *Quinine hydrochloride with urethane* is available in 2-cc. ampules, which is the top dose that may be injected in one site or at one sitting; the frequent occurrence of cinchonism would seem to indicate a 1-cc. maximum as safer (immediate reaction: tingling, cyanosis, edema, bronchial spasm—antidote: epinephrine, toxic reaction, usually occurring after several hours: tingling, neuralgia, vertigo, visual and aural disturbances, delayed reaction, after several days: malaise, itching eruption, fever, protracted course). Quinine does not cause injection pain or cramp nor after pain, but it does cause slough outside the veins. Schmier (1937) also charges it with being chief offender in production of the slough which sometimes appears several weeks following the injection of a thin walled vein, a type of "postobliterative" slough which is said not to be due to perivenous infiltration. Menorrhagia, premature menstruation, and bronze discoloration of the skin are recorded against the drug also. *Sodium salicylate*, used in quantities of 1 to 5 cc. of 20, 30, or 40 per cent solution, causes severe pain on injection and

slough if injected outside the veins. Occasionally it also causes more or less severe salicylism. *Sodium chloride* is used in 15 to 30 per cent concentration and in amounts from 1 to 10 cc. It causes severe cramp on injection and slough outside the veins, but Schmier has known patients who preferred this brief cramp which is less severe than that caused by salicylate, to the long drawn out pain sometimes induced by morrhuate. Some men, however, such as Riddoch (1034) find the salt altogether too variable in its sclerosing effects. *Invertose*, *sucrose* and *dextrose* are used in concentrations of 50 to 75 per cent and amounts of 2 to 10 cc. or more. Systemic reactions are not to be feared with these sugars, but they do give rise to some pain on injection and will cause slough outside the veins. Their sclerosing effect does not seem to be uniformly obtainable.

TECHNIC OF SINGLE INJECTION METHOD

A 5 or 10-cc syringe with a sharp, short bevel 22 to 26 gauge needle is used. Most injections have been given with the patient sitting on a table or standing on a chair in order to have the fullest possible distention of the vein. Time has shown that there is no advantage in segregating a portion of the vein; the site is merely selected, the skin treated with an antiseptic, the needle introduced and the plunger withdrawn to be sure that the vein has been entered and the injection slowly made (some men like to express the blood upward before, and hold it out of the way during the injection). Afterward a tight bandage is placed over the site and the patient instructed to indulge in no rubbing or massaging. Injections, usually made at intervals of one week, begin with the distal veins and work upward (except when there is ulcer—see later). In the intervals between injections it is usual to keep a spiral elastic bandage on the limb; the patient is of course to remain ambulatory.

If it is suspected during the injection that fluid has escaped from, or been placed outside the vessel, injection must cease at once and 5 to 10 cc of 1 per cent procaine solution should be immediately injected subcutaneously. The injection of 5 cc of the patient's own blood from a neighboring varix has also been recommended as diluent and to aid absorption through the inducing of marked hyperemia, I do not know how well this works. Dry heat may also hasten absorption. If slough occurs it is said to be best to excise it early—in the operating room, not in the dispensary or office.

Latterly, the empty vein technique has gained many adherents. The steps are (a) apply a soft rubber tourniquet proximal to the site for injection with the patient standing (Benoett-Jones, 1036, places the blood pressure cuff on the lower third of the thigh and inflates to 180 mm.), (b) then have her lie down and place the heel on a small block or box, (c) when entry is made the tourniquet is released and the injection made after the vein visibly collapses, (d) the limb remains raised until the elastic bandage is applied.

TECHNIC OF MULTIPLE INJECTION METHOD

In an attempt to shorten the total time of treatment many points along the course of a vein are injected at a single sitting. Horlick (1035), who has slightly modified McPheeter's original technique, proceeds as follows. The patient is placed in an erect position and the points where injections are to be made are marked with mercurochrome solution or tincture of iodine so

that one may know where to inject when the veins are subsequently collapsed. The patient lies down and the extremity to be treated is elevated and stripped of blood. Two tourniquets are applied about six to eight inches apart, starting at the foot or ankle. These must not be applied so tightly as to cut off the deep circulation, for serious trouble might ensue from the sclerosing solution finding its way to a corresponding segment of the deep circulation. After this, the leg is lowered and the points previously marked are injected between the tourniquets with the solution to be used. Pads of gauze are strapped over each puncture wound. This done, the distal of the two tourniquets is removed and the leg again elevated and stripped of blood. The tourniquet previously removed is then applied about six to eight inches above the one left in place and the leg lowered. This segment is then injected as was the lower one. This procedure is followed up the leg and thigh until the veins are injected to the groin. The most proximal of the tourniquets is left in place and the whole extremity is firmly and evenly bandaged from toes to groin. The ace or elastoplast bandage is ideal for this purpose. In our clinic, because the cost of these latter is prohibitive, we use sheet wadding and ordinary bandage with satisfactory results. When the bandage is applied the tourniquet is removed. By this means the veins have been injected while collapsed and have been kept collapsed, as nearly as possible, by the bandage. The resulting thrombi will thus be smaller in diameter. It is advisable to keep the bandage in place until the next visit to the clinic. At the ensuing visit, small varicose veins, so-called 'pick ups,' missed at first, may be individually injected without the use of tourniquets. If the veins of both legs were varicose and only one done at the first visit, the other may be done at the same time as the 'pick ups'."

TREATMENT OF PHLEBITIS

Cases of phlebitis vary greatly in severity from those with negligible local and no constitutional signs to those having attacks of rapidly ascending thrombosis, with marked local inflammatory reactions, high fever and other symptoms of sepsis, and even in rare instances embolism. It is the consensus that in cases in which there are constitutional signs the patient should be in bed with the leg elevated and hot boric acid dressings applied, the use of cold dressings or the ice bag has fallen into disrepute because cold is alleged to promote thrombosis and devitalize tissues—Homans (1938) says he has seen frostbite from the application of ice bags. With the subsidence of symptoms, an Unna paste boot, or elastoplast bandage or elastic stocking is applied, and the patient cautiously allowed to become ambulatory, recurrence of fever and other general symptoms, or significant changes in the white count and sedimentation rate, compelling return to bed. In the less severe cases with little inflammatory reaction and no constitutional symptoms, tight bandaging as above, and the patient remaining on his feet, is considered adequate treatment. However, there are some dissenters from this plan of treatment. Wright (1936), who has certainly had abundant experience, believes that if the elastoplast pressure is reinforced by sponge rubber strips placed beneath it along the tender inflamed veins, even patients with fever may be allowed to continue out of bed, indeed, his view is that the more severe the superficial phlebitis the more essential it is to keep the

patient ambulatory to prevent embolism and deep thrombosis. Payne (1936) says that in the beginning if there are signs that the process is a septic one, the internal saphenous vein should be ligated at once at the saphenofemoral junction. He also seeks to hasten recovery in extensive cases by excision of the inflamed mass of veins and the overlying adherent skin at the end of a month, but Wright firmly opposes this, and I am sure many others agree with him. In protracted and recurrent cases, a most exhaustive study of the patient must be made, particularly seeking to eradicate foci of infection elsewhere.

Until recently most men in this field have been agreed that injection treatments should not be given in either leg while there is an active area of phlebitis present in one of them, the feeling being that an arbitrary waiting period of six months after subsidence is not a bit too conservative. Latterly, however, there have been some dissenters from this viewpoint, for example, Biegeleisen (1936) and Edwards (1938), the latter taking the position that since this type of phlebitis is essentially bland and both the varices and phlebitis will recur after the acute process is over, the indicated procedure is immediate treatment by the combined ligation-injection method.

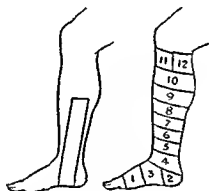
TREATMENT OF VARICOSE ULCER

When I was in residence at the New York Skin and Cancer Hospital a certain number of years ago, we used to treat ambulatory cases in the clinic with salves and no hope, or an occasional Unna paste boot, but when we could get a bed in the house and a patient who could occupy it for the requisite number of weeks or months, we did cure them. The patient was put to bed, the ulcer cleaned, and a gridiron of narrow adhesive straps criss crossed over it. Various wet antiseptic dressings were then applied continuously in the beginning, and later the exuberant granulations were cut down with the silver nitrate stick, which was also used upon occasion to touch up the sluggish edges here and there. They got well at last (shall I ever forget the old Irish woman who knitted sweaters for the staff, twice round!), but I do not think the dressings had anything to do with the result. The more blithely they went out, the more disgruntled they returned, however, for we were not doing enough with the recumbent position, and in those days we hadn't begun injecting the veins to attack the matter at its roots. Now all that is changed, for the majority of ulcers gradually heal after successful obliteration of the veins (87 per cent in Payne's [1936] extensive series), and those which do not are apparently in most instances healed by one of the two bandaging methods described below.

The Occlusive Compression Bandage—The advantages of this method, developed by Wright, in England, are the following: (a) the varicose circulation is abolished, forcing blood through the capillaries and thus reestablishing aeration of the tissues, (b) edema is reduced, thus bringing the edges of the ulcer closer together and pressing the raised margins of an indurated ulcer down flat, (c) delicate granulations and new epithelium are not only protected from dressing trauma, but the wound is actually dressed in its own secretions—the “pansement spécifique” of Besredka, (d) pain is abolished in the majority of cases, (e) work and exercise aid rather than hinder the cure, (f) cure is rapid—“frequently an ulcer of the size of the palm of the

hand, if of short duration, will heal within seven days, (g) the ulcer is cleaned more quickly than by antiseptic methods and fetor rapidly disappears, (h) varicose veins that had been deeply buried in edema are brought to the surface and rendered injectable, (i) the scar is supple without adherence to the bones, (j) expense is saved, (k) no special training or skill is required to apply the treatment

Details—(1) The uppermost veins are injected (Wright uses 5 per cent sodium morrhuate) from above downward (2) The leg is then wound with an elastic adhesive bandage (elastoplast) very firmly and evenly, the tightness of the winding being proportional to the swelling and induration, sometimes using practically all of one's strength—"the almost invariable cause of failure is the looseness of the bandage" Begin winding near the toes, having first put in place the stirrup as shown in the accompanying sketch (3) No treatment of any kind is applied to the ulcer, neither eczema phlebitis nor periphlebitis being considered a contraindication indeed, Wright considers associated arterial disease and diabetes to be practically the only contraindications to the entire treatment (4) If the ulcer is of the painful type, aspirin powder is blown in with an insufflator and the patient is given a



hypnotic for a few nights the latter not so much for the pain but because "she has fed the ulcer with salves, antiseptics, lint and gauze for so long that she thinks terrible things are happening under the bandage" The pressure over the ulcer, if it is a particularly painful one, is sometimes increased by applying a small firm absorbent felt pad to the ulcer bed and placing another pad of sponge rubber between it and the turns of the bandage, specially useful is this procedure in treating ulcers in the sulcus under the malleolus where the bandage does not grip very tightly (5) The patient is instructed to wash off the discharge if it seeps through, with a nailbrush and soap and to protect the clothing with a dressing over the weeping area and also to wear a long stocking over the whole *Work and as much walking exercise as possible are mandatory* (6) The subsequent visits are dependent upon the size and location of the ulcer (over the malleolus, movements will loosen the bandage, copious discharge will necessitate frequent changing, disappearance of edema will also require reapplication) (7) Upon each removal of the bandage the veins are injected again in the previous order and also any others that have become accessible, and if the ulcer is large and a good sheet of granulations has developed grafts are inserted under them

on the fibrous bed—insinuation of small implants, darning in threads of skin or injecting a suspension of skin in saline "Grafting may be repeated and it is always well to have a graft waiting in the center of the last patch of ulcer to receive the edges as they close in, otherwise there is often an annoying delay at the last" (8) Finally, when the ulcer is healed and all veins obliterated, the former often being accomplished first, an Unna paste hoot, or an elastoplast bandage is used as long as seems necessary to consolidate the cure

Wright finds that eczema may develop under the bandage, or if previously present may get worse during treatment, however, so far as the patient will permit, he ignores it and is often rewarded by disappearance of eczema, ulcer and edema simultaneously. Failing, he employs interchangeably bandages impregnated with rivanol 1 1000, ichthyol 5 per cent and aluminum acetate 5 per cent, sometimes he uses zinc oxide ointment. Blisters developing under the bandage do not cause him to alter the treatment, overlapping each turn of the bandage with two thirds of its width, plus the greatest care in application, has usually avoided cutting with resultant linear ulceration in very edematous legs

Rubber Sponge Supportive Bandage—This method of therapy developed by McPheeters has been called by him the "venous heart" treatment and rests on the belief that the patient's heart will pump fresh arterial blood filled with oxygen and tissue food to the ulcerated area but that the circulatory apparatus must be artificially aided to carry off the products of combustion and ketosis which cause the local acidosis and tissue death. To this end he applies a rubber sponge tightly to the ulcerated area and then causes the patient to walk a great deal, so that with each step the elastic sponge performs a "systole and diastole" by which serum, lymph and venous blood are actively pumped away from, and arterial blood into, the affected tissues at the same time that all the advantages of constantly applied firm pressure are obtained. Unless the patient exercises he will suffer intolerable pain, with exercise he will find that the normal soreness and the edema rapidly disappear and "ideal conditions are maintained for the ulcer healing the end results are reached in a comparatively short period, and the patient continues on at work during the entire period" The treatment is of course absolutely contraindicated in the bedridden

Details—(1) Cleanse the skin and ulcer area with gauze and benzine and apply 10 per cent silver nitrate to the ulcer, which will stimulate but is of no value at the first dressing of a badly infected and necrotic ulcer (2) Apply some ointment that will *remain soft* to the ulcer, cover it with fluffed gauze and 4 layers of sheet wadding or cellucotton (3) Bandage in place directly on the ulcer a good grade rubber bath sponge (firmest possible) that is 1 inch larger than the ulcerating area, using a plain 3 inch gauze bandage and being careful that the whole does not slip to one side (4) Apply a 4 inch Ace bandage from just below the knee to the toes, over the sponge and dressing, applying it as a double figure-of 8 about the foot and ankle (5) Convince the patient of the absolute necessity of walking as much as possible (6) The dressings are to be changed as often as necessary to prevent saturation "Every two days is preferred. The rubber sponge can be boiled up and used again when soiled, but should be discarded as soon as it has lost its 'kick' and has become firmly pressed together" After

healing, the subsequent treatment is practically the same as in the method of Wright (see above)

Mecholyl Iontophoresis—In cases which have been especially resistant to the above types of treatment, or when one of the several contraindications has made injection treatment impossible, several men (Sayler *et al.*, 1936, Murphy, 1937, Sokolov and Meyers 1939, Montgomery, 1941) have reported more or less success by keeping the patient actively ambulatory, using no other dressing than a bit of petrolatum on gauze if it makes the patient more comfortable, and resorting to iontophoresis of mecholyl (acetyl β methylcholine) solution. The following is Sayler's original technique reinforced: asbestos paper soaked in 0.5 per cent solution of the drug is wrapped around the foot and leg as high as the knee, the ulcerated area not being covered during treatment until it has acquired a firm scab. A malleable metal plate is placed over the wet paper, not applying it over the ulcerated area and connected to the positive pole of a galvanic machine, a regular large moist pad electrode placed under the back, is connected to the negative pole. The current is turned on and slowly increased to 20 to 30 milliamperes and then slowly reduced before turning off, treatments lasting twenty to thirty minutes are generally given two or three times weekly. The local reaction consists in warmth, prickling, blush, gooseflesh, sweating, elevation and fall and subsequent elevation in temperature. A general reaction with circulatory, respiratory and gastro intestinal symptoms predominating may be stopped at any time by an injection of atropine sulfate.

The Unna Paste Boot—This dressing several times referred to above is made and applied as follows: (a) Stir 100 Gm. of gelatin into 400 cc. of water and allow to stand overnight, then bring to a boil and add 100 Gm. of zinc oxide and 400 cc. of glycerin which have been previously rubbed together to smoothness, boil while stirring for fifteen minutes. (b) Cool to a bearable temperature, or beat to same if the paste has already hardened, and paint with a wide camel's hair brush over the ulcerated area which, together with the leg, should have been thoroughly cleansed first; the latter shaved also. Now apply a spiral bandage and a second coat of paste and repeat until the desired rigidity is attained. The entire space from ankle to knee is usually covered. Isaak (1940) says that the ready made zinc oxide gelatin bandages, nowadays available, may be satisfactorily substituted in the above procedure. In the older type of treatment, when the secretion began to seep through a window was cut over the ulcer and antiseptic and cleansing applications made directly to the raw surface, the leg being held fairly stiffly encased in the paste boot, now, as described above, the Unna dressing is more often applied on the dry surface after healing of the ulcer. When wet dressings are being applied the boot is usually changed every two weeks, every three weeks at least.

Thiamine for Pain—In a few individuals the pain of varicose ulcers is very severe and, since one does not dare employ opiates, it is often difficult to give relief, this may be particularly distressing when the ulcer is yielding very sluggishly to treatment. In 10 such patients, Ochsner and Smith (1940) gave thiamine hydrochloride (vitamin B₁) in doses of 3 to 15 mg., in one instance 30 mg., daily, in all but 1 patient there was definite relief in a few days and 8 had complete subsidence of their symptoms; definite increase in the healing of the ulcer was noted also in half the cases. The authors felt from

this experience that 5 mg thrice daily should be the beginning dosage, to be doubled if results are not obtained. No explanation of the action of the vitamin in these cases is at hand

ESSENTIAL HYPERTENSION

(*Hyperpiesis*)

Permanent elevation of the blood pressure without known cause is a disease of high incidence and great seriousness. Studies of a number of independent investigators have shown that it is present in about 16 per cent of the population in the United States and Canada, a figure which is probably too high to hold for England and the Continent, since the reflection of the thought of European physicians in the literature does not show them preoccupied with the disease, the incidence in other parts of the world is not accurately known to me, but the assumption of rarity in China, India and tropical lands everywhere is probably gratuitous, for a number of physicians have informed me that they see numerous cases in these countries. The matter is ripe for investigation, all the more in that the result of statistical studies might help to disabuse us of the notion, whose validity is far from proved, that it is the kind of life we lead in America that causes the disease. Here with us hypertension ranks with tuberculosis and cancer as causes of death, the actual exitus being due to cardiovascular disease closely connected with the hypertension in the vast majority of instances—specifically in 72 per cent of Paul White's (1936) large series of cases.

The symptoms which bring the patient—usually between forty and fifty, as likely perhaps to be a man as a woman, often broad-chested and obese—to the physician, and thus lead to discovery of the high blood pressure, are usually disturbances in kidney function, cardiac and respiratory complaints, vertigo, dyspepsia, bleeding from the mucous membranes, loss of weight, retinal hemorrhage, persistent morning headaches, unusual drowsiness, and transient palsies and aphasia. The height of the systolic pressure varies greatly, it may be only 160 or it may rise above 300. Of course the height of the diastolic rise depends upon the state of the heart and vessels, hypertrophy and arteriosclerosis being usually early complications of the malady, but the impression that a constant diastolic pressure of 120 is not compatible with more than two years of life is contradicted by many records. Indeed, Flaxman's (1936) statistical study, like the earlier classical one of Janeway, indicates the necessity for great caution in prognosis in any individual case, for a small but significant number of his patients were still alive five to twenty years after appearance of the first symptom. Murphy, Grill *et al* have shown that the histologic quite like the clinical manifestations in "malignant" cases differ from those of ordinary cases in degree only.

The etiology of the essential hypertension syndrome is still obscure, though great strides have been made in recent years in the study of hypertensive states induced in experimental animals, Goldblatt and Page, and their respective associates, being chiefly responsible for these advances. From

these studies it seems that the kidney produces a substance, renin, which is converted in the normal blood plasma into a second substance, angiotonin the latter being an agent which causes vasoconstriction (in the kidney there is particularly constriction of the glomerular efferent arterioles) There is also evidence that the normal blood contains a substance which inhibits the action of this vasoconstricting agent Page (1941), and Grollman *et al* (1940), have been studying the effect of kidney extracts thought to contain the inhibitor agent, but they feel that the subject is still in the experimental stage and not ready for general application in practical treatment

THERAPY

Treatment of this serious malady must remain entirely unsatisfactory until the cause or causes of the rise in pressure are elucidated The measures to be described below are designed to lower pressure solely in an attempt to prevent the deadly sequelae of a maintained hypertension—heart failure, apoplectic stroke, kidney dysfunction Evans and Loughnan (1939) made a very careful study of a large number of drugs in comparison with placebos in 70 patients, their results, taking into account the wide "normal" variations of blood pressure in hypertensive patients, of which Ayman wrote in 1931, were the following (a) none of the drugs were of value in lowering blood pressure, (b) the following only were of value in effecting symptomatic improvement irrespective of the blood pressure, which indeed was often in a high phase at the time iodides, bismuth subnitrate, bromides, barbiturates and potassium thiocyanate However, the interesting studies of Ayman and Goldshme (1941) show that the patient's blood pressure when taken at home by himself or a member of his family is consistently and considerably lower than when taken by the physician in office or clinic—which would indicate the possibility that our treatment measures are more effective than office records show Perhaps it is well to point out also that no treatment is often the best treatment, at least for a while, i.e., some patients will only be made unnecessarily miserable instead of being helped if it is hinted to them at all that their blood pressure is high

Rest—I quote Mosenthal "The best available means at the present moment to reduce the blood pressure in essential hypertension is to obtain nervous relaxation in the patient This is glibly said but hard to accomplish for it means untold effort on the physician's part and limitless cooperation by the patient Occupation, home life, social obligations and many other factors must be studied and their rough corners rounded off The regulation of occupation, family relations and other personal affairs must remain an individual matter It is a good plan to have the patient visit the office once a week and talk over such topics for a few minutes Eventually a way out may suggest itself A good routine of relaxation is one or two hours' rest after lunch and at least eight hours in bed at night In severe cases, one day a week in bed may be recommended At times, more or less prolonged rest in bed may be of value"

All else is of quite secondary importance compared with the necessity to accomplish nervous relaxation in the patient If this cannot be achieved without drugs, there should be no hesitation in employing the sedatives, see the article on Insomnia Allen and MacLean (1940) believe it might be advisable

to investigate the value of raising the head of the bed in attempting to prevent the early morning headaches

Exercise—Evidence is accumulating that sedentary individuals are more subject to hypertension than physically active persons. Gunewardene (1935) has made the interesting observation that in India hypertensive disease rarely occurs among rickshaw runners with their strenuous exercise and long hours but that it is common in certain social groups who lead sedentary lives with habitual overeating. Many years ago Janeway found that exertion, even as strenuous as in tennis playing, was helpful in younger persons. Mosenthal gave it as his opinion that moderate exercise as walking, golfing or restricted setting up calisthenics, serves to keep the voluntary and cardiac muscles in better condition and promote more satisfactory well being than if a more physically restricted course is pursued. One may guardedly lay down the principle then, that exercise within the limits of cardiac power is beneficial.

Diet—All the dietary restriction that the hypertensive patient needs is in quantity if he is obese or if there is a gobbling fulsome tendency in his family, for every bit of evidence in favor of any particular *qualitative* change in diet it is possible to find a sufficient amount of recorded contrary evidence to invalidate the whole contention.

Alcohol and Tobacco—Alcohol in great moderation does not seem to be harmful, indeed it seems to "smooth out" some of these temperamental people. Smoking is sometimes demonstrably harmful.

Cathartics—Alvarez and associates demonstrated a number of years ago that constipation has no effect on blood pressure in men, and that in women it is associated with lowered pressure, findings which should dispose once and for all of the "intestinal auto-intoxication" myth. That a certain number of patients die in the lavatory is taken to indicate that straining at stool is to be combated at all costs, be it noted, however, that no one has proved this point.

Venesection—Bleeding as the sheet anchor of treatment has of course been abandoned but many physicians still resort to it in the plethoric individual when heart failure or apoplexy is threatening. Elliot, who reviewed the subject some years ago, concluded that "a good bleeding will sometimes postpone the breakdown." Mosenthal (1940) has recently expressed himself in favor of frequent moderate bleedings (200-300 cc) in patients who are inclined to plethora.

Intravenous Injection—The modern method of depleting the circulation and thus relieving the brain is to inject hypertonic solutions but the superiority of this method to venesection does not seem to me to have been conclusively shown. The solution currently in greatest vogue is 50 per cent *sucrose*, injected intravenously in an amount of 300 to 500 cc daily. It seems that diuresis begins in two hours and lasts usually for six hours and that there occurs prompt reduction in spinal fluid pressure with gradual return to the previous level in eight to twelve hours, blood pressure is little affected. Relief from such aggravating symptoms as headache, vomiting, vertigo, twitching and dizziness has been reported. But Anderson and Bethca (1940) found distinctive renal lesions after the administration of such *sucrose* solutions in 6 cases, and similar lesions have been produced in experimental animals. *Magnesium sulfate* is also injected intravenously, but its use in nephritic patients would probably be dangerous. Average dosage is 10 cc of

10 per cent solution not oftener than once daily. Lissner (1934) finds these injections exerting a marked influence upon the eye changes, aiding absorption of exudate of retinal hemorrhages, and adding hope of prevention of threatened blindness. Murphy *et al.* (1941) caution that intravenous injections of any sort must be given extremely slowly in patients with any type of cardiovascular disturbance.

Iodides.—Sodium or potassium iodide, 5 to 15 grains (0.32–1 Gm.) three times daily, is employed by many physicians in all cases even though there is no evidence of a syphilitic involvement. I think we have very little scientific warrant for this sort of routine "alterative" medication, though the statement, "it can't do any harm," is probably a true one. Parkinson and Hoyle (1934) point out interestingly that in cases benefited there may be an underlying thyrotoxicosis. However, in the study of Evans and Loughnan (1939), referred to in the beginning of this section on therapy, iodides were one of the small group of drugs that was effective in inducing symptomatic, though not blood pressure, improvement.

Digitalis.—When heart failure threatens or occurs it should be treated just as at any other time. The additional practice has arisen in the last few years of attempting to forestall the cardiac catastrophe by placing the patient on digitalis before the heart shows signs of failing; full digitalization is not attempted usually, the patient being placed merely on maintenance doses after a short period of somewhat higher dosage in the beginning. The reader is referred to the discussion of chronic nonvalvular heart disease.

Nitrites.—Erythrol tetranitrite and mannitol hexanitrite are the longest lasting in their effect upon the blood pressure and are therefore to be preferred. They are obtainable in $\frac{1}{4}$ - and $\frac{1}{2}$ -grain (0.015 and 0.03 Gm.) tablets; the effective dose is $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.) every four to six hours or as indicated. Both preparations are rather expensive.

Sodium nitrite is second in point of duration of effect to the above two salts, but it has the disadvantage of causing gastric disturbances in most individuals. It is given in capsule in a dose of 2 to 3 grains (0.13–0.2 Gm.), often combined with an equal amount of sodium or potassium iodide, at intervals to be determined in each case. The enteric-coated tablets, now available, are probably much less irritating.

Nitroglycerin is the least durable in its effect upon the blood pressure, but it is the preparation often preferred for the following reasons: it does not usually disturb digestion; it may be conveniently prescribed in the form of hypodermic tablets of $\frac{1}{100}$ grain (0.0006 Gm.), which are not volatile, do not quickly deteriorate, and may be easily dissolved under the tongue. The dose is one or more tablets as required. The drug is much cheaper than the erythrol or mannitol salts. Lueth and Hanks (1938) have reported severe reactions in a number of their patients using nitroglycerine: nausea, vomiting, collapse and the involuntary passage of urine; such reactions are also mentioned under Coronary Disease.

Amyl nitrite is very little used in the treatment of hypertension because of the brief duration of its effect.

Stieglitz found the nitrate radical of bismuth subnitrate liberated as the nitrite radical by bacterial action in the intestine and the nitrite slowly and evenly absorbed to produce hypotensive action. Bismuth subnitrate is given in doses of 10 grains (0.6 Gm.) three times daily in capsules. Stieglitz (1936)

reported very good results in a large number of patients, but both Ayman (1932) and Bruen (1934) were unable to duplicate the findings in rigorously controlled series, Evans and Loughnan (1939), however, in the study referred to in the beginning of this section on therapy, found hydralazine one of the small group of drugs that was effective in inducing symptomatic, though not blood pressure, improvement.

Thiocyanates (Sulfocyanates).—It seems to me that the sodium and potassium thiocyanates have had a long enough time in which to prove their right to a place in the armamentarium of essential hypertension, and that they have failed to meet the test. To be sure, they seem oftentimes effective (at least they are so reported) in lowering the blood pressure, and they were one of the small number of drugs found effective by Evans and Loughnan (1939) in inducing symptomatic, though not blood pressure, improvement, as noted in the beginning of this section on therapy in hypertension. But the following facts seem to me to require most careful consideration.

(n) The foremost advocate of thiocyanate therapy, Barker of Northwestern University, freely admits the toxic actions of the drugs, but feels that these actions may be grouped as mild and severe, and that the severe effects are seen only when the proper blood cyanate level has been exceeded.

(b) It is considered that the cyanate at level which best effect is obtained is 8 to 14 mg per cent (the upper figure has been recently reduced by Barker, 1941, to 12 mg) and that above this level is the danger zone into which one should not go. Barker's routine, according to Wald *et al* (1939) of his group, is to administer two doses of 5 grains (0.3 Gm) daily for three days and then do a blood cyanate determination if the patient is in hospital, those not hospitalized are given ten doses within a week and the first cyanate determination is done on the eighth day. But in their experience maintenance dosage has varied from 5 grains (0.3 Gm) a week to as much as 15 grains (1.0 Gm) a day, and fluctuations in dosage occur frequently in many cases. Obviously, this means that if the physician is to know at all times the precise cyanate level of his patient—which Barker insists upon—he is obliged to have cyanate tests performed at very frequent intervals indeed.

(c) Wald *et al* list the following mild reactions: sensations of weakness and fatigue which occur in 75 per cent of cases and are said usually to disappear after several weeks, frequent occurrence of aching and cramping of the calf muscles, increased nervousness and irritability in some instances (but sedative effects are also sometimes seen), toxic dermatoses of various sorts (severe exfoliative dermatitis has not been seen by them but it has by others), enlargement of the thyroid, various gastro-intestinal disturbances. As severe reactions, seen only when the safe blood level has been exceeded, they list severe gastro-intestinal disturbances, vascular collapse, cerebral thrombosis, slurring speech, aphasia, convulsions and delirium, angina pectoris, death, usually preceded by coma and convulsions.

(d) Despite the assertions of the proponents of the use of these drugs that serious reactions are not to be feared if the dosage is such as to keep the blood cyanate level under 14 mg, such reactions have been recorded on low blood levels. (a) Robinson and O'Hare had reactions in 38 per cent of their 75 patients, serious reactions occurred in 6 cases and in 2 of these within the "safe" level, (b) Greene and Snow (1939) report a very severe reaction in a patient who had been on the drug only a few days and had

not had a level above 3.7 mg, (e) The fatal reaction in Garvin's (1939) patient began when the cyanate level was within the safe range, (d) Blaney *et al* (1941) found toxic manifestations common above 15 mg but not invariably present even with twice this concentration, while in 1 of their 20 patients serious intoxication occurred at a concentration between 6 and 7 mg, (e) Blaney *et al* examined their data for criteria to aid in the selection of patients suitable for thiocyanate therapy, including considerations of age, duration of hypertension, sex, severity of hypertension, cardiac and renal complications, retinitis test of vascular reactivity, they found nothing that would seem to serve as a useful guide

Miscellaneous Drugs—I do not feel, from close study of the rather large literature available to me, that any of the following have yet been shown to have worth in hypertension bistamine, acetyl β methylcholine (mecbolyl), adeosine and adeylic acid, tissue extracts cucurbitaria, estrogenic substances, male hormone, oxygen

Surgical Procedures—In the preceding edition of this book I stated my feeling that the surgical treatment of essential hypertension did not rest upon a sound scientific basis, since that time the surgical literature of the subject has become rather bulky, but my opinion in the matter—purely 'armchair' to be sure—has not changed. Indeed it seems to me highly entertaining that Volinn and Flaxman (1939), at Cook County Hospital have found that the symptomatic relief and blood pressure reduction resulting from nonspecific surgical measures (*i.e.* hysterectomy prostatectomy, cholecystectomy) in the presence of essential hypertension are similar to and some times better than those resulting from specific surgical measures (*i.e.*, extensive sympathectomy, splanchnic nerve resection celiac ganglionectomy)

ARTERIOSCLEROSIS

Arteriosclerosis is a disease characterized by hyperplastic, hypertrophic, fibrotic, calcareous and necrotic changes in the vessel walls, resulting ultimately in diminution of normal elasticity plus weakening and deformity. Apparently many individuals can remain in excellent general condition with tortuous and quite 'hard' arteries, but they carry always the potentiality of experiencing a vascular crisis—cardiac, cerebral, gastro intestinal peripheral, etc. Until such accident occurs, the following are about the only aids in determining the state of an individual's arteries (a) a gradual loss of mental and physical vigor in an elderly individual otherwise apparently healthy is looked upon as presumptive evidence of generalized arteriosclerosis (b) if ophthalmoscopic examination reveals normal or nearly normal retinal arteries, and if there is extensive drop in diastolic blood pressure upon inhalation of amyl nitrite (Stieglitz test), one may assume that there is very little hardening of cerebral vessels, (c) arteriographic and oscillometric studies may make possible the differentiation between vasospasm and organic arterial disease in the peripheral vessels, (d) intermittent claudication—pain

in the calves, produced by exercise but not by standing, and relieved by rest—is indication of advanced arteriosclerotic or thromboangitic occlusive involvement in the extremities

In most cases the blood pressure is not raised, but when it is, that is to say, when essential hypertension and arteriosclerosis are coexistent, then the prognosis is much more grave. The following is the order of frequency with which most pathologists have found the organs to be affected, those organs most frequently affected being also most markedly affected: spleen, brain, kidneys, adrenals, pancreas, heart, gastro-intestinal tract, lungs, liver and diaphragm.

Some investigators are beginning to state in a tentative fashion that a definite hereditary factor is responsible for the development of this condition in some individuals much earlier than in others living under the same stress and strain. Diabetes appears with suggestive frequency in connection with this disease, but what direct relationship it or any other factor such as the alleged disturbance of cholesterol metabolism, as principally championed by Leary, have to do with the etiology remains unknown.

The great anatomist Scarpa (1747-1832) was the first to record the opinion that arteriosclerosis is a disease of the inner coats of the arteries.

THERAPY

For those victims of arteriosclerosis who suffer general mental and physical deterioration there is nothing to do save direct their lives in as pleasant channels as possible, nor can one write much of an edifying nature about the prevention of the condition. To avoid the competitive hurly-burly of life as much as possible, to avoid too quick returns to full activity after attacks of the acute diseases, to submit to the fullest treatment for the chronic affections, and to select one's parents as carefully as may be, are all measures of presumptive value. No form of dieting, not even that type which is called 'low-cholesterol' (omit brains, butter, egg yolk, fish and fish roe, kidneys, lard, liver, meat, oysters, poultry, suet and sweet breads) is rationally indicated. In effect the treatment of localized arteriosclerosis is really the treatment of chronic nephritis, coronary thrombosis, congestive heart failure, hemiplegia, etc.—entities dealt with elsewhere in the book. Where there is intermittent claudication and peripheral vascular occlusion with gangrene, the treatment is essentially the same as in thromboangitis obliterans, except that elderly arteriosclerotic patients may be expected not to tolerate typhoid vaccine injections so well as the younger patients with Buerger's disease, and one would think that radical operation should be approached in this group with great diffidence. Bernheim and London (1937) find cessation of smoking equally demanded in both diseases. It is possible that in arteriosclerosis one or other type of passive vascular exercise may finally be shown to be of somewhat more value than in thromboangitis obliterans, but so far I have seen no published study proving this to be so in a large series of cases.

HEMIPLEGIA

The three chief causes of hemiplegia are hemorrhage, embolism and thrombosis, but it will be convenient to include at this place also a few measures more particularly applicable to paraplegia due to severe cord injury. Whether the patient has bled or is bleeding at the time he is first seen in a typical "stroke" is by no means easy to say, but it is the time honored custom to assume that hemorrhage is occurring and that something must be done to stop it. To this end it is usual to raise the head and put an ice-bag on it and lower the feet and place them in a warm mustard bath. Most patients who have bled sufficiently to have hemiplegia will die very soon and these measures will probably do nothing to stay the end, however, it is little short of cruel to the anxious family merely to stand by and do nothing and thus these manipulations are amply justified on the basis of the activity and participation of a number of individuals which they necessitate. Another bustling type of treatment is autohemotherapy withdraw 25 to 30 cc of blood from a vein and immediately reinsert it into the buttock, it is well to have a few cubic centimeters of 25 per cent sodium citrate solution in the syringe as the blood is drawn. Venesection to reduce blood pressure is now discountenanced, lumbar puncture and drainage is probably no more justified, since coma in apoplexy is nowadays thought to be caused largely by cerebral edema which is not remedied by either of these depleting measures. The use of stimulant drugs is contraindicated. After the cataclysmic event, and whether the patient has or has not recovered consciousness, and regardless of the hemorrhagic, thrombotic or embolic nature of the acute episode, the therapeutic problems are posed by the residual paralysis and their complicating sequelae. Symptomatic treatment is all that is available in the present state of our knowledge many of the following measures are really nursing details.

Care of the Skin—This patient, like any other, is to have a daily soap and water bath. The best way to minimize the damaging effects of sustained pressure upon bony prominences is to have the patient shifted from one position to another—every two hours is not a bit too often. Water cushions next best air cushions and lastly cotton rings, placed to advantage, will help distribute the pressure, pillows under the back and knees are also helpful. Sheets and bedclothing should be kept absolutely free from wrinkles and crumbs or other gritty substances, this is very important. In shifting the patient he is to be lifted and not shoved or pulled about. If he has free use of his arms and is assisting in the nursing by pulling on a rope to raise the upper part of his body, Cohen (1935) points out that special attention must be given to the skin of the buttocks and lower limbs which are much chafed by such movements. In most instances frequent gentle rubbing of the back with 50 per cent alcohol (not denatured), followed by light application of talcum powder, is good treatment, 1 ounce (30 Gm) of alum added to the pint (500 cc) will make the lotion still more drying. But judgment must be exercised for there are cases in which the skin, already excessively dry, will be better treated by the application of an ointment, Fantus (1935) offers the following, which looks very much like a shotgun prescription to me despite its alleged popularity with the nurses at the Cook County Hospital.

R	Zinc stearate	5 00
	Tincture of benzoin	5 00
	Scarlet red ointment, 5 per cent	0 25
	Hydrous wool fat	30 00
	Liniment of camphor	180 00
	Mutton tallow	500 00

Melt the fats, add the camphor liniment, and when the mixture has almost cooled beat in the tincture of benzoin and the zinc stearate until a creamy mixture is secured

Label After each cleansing, apply a very small amount of this ointment during the back rub if the skin is harsh and excessively dry (to prevent bed sores)

The application of elastic adhesive plaster (elastoplast), not stretched before applying, or a dressing of flexible collodion to a threatened point is said to prevent sometimes the development of a bed sore. The greatest difficulty lies of course in preventing maceration of the skin in a patient who is incontinent. Several layers of newspapers on top of the sheet (which has a rubber sheet beneath it to protect the mattress), with absorbent material such as oakum between the papers and the body, is the measure usually resorted to, sometimes such a dressing may be held in place diaper wise. In the worst cases a specially divided mattress may be employed, or a hole may be cut in the mattress at hand and the fluids directed into a pan on the floor by rubber sheeting draped in the hole. In some cases of paraplegia, especially where there has been severe damage to the cord, the patient suffers paroxysms of sweating which of course only add to the dangers of maceration, atropine sulfate, $\frac{1}{16}$ grain (0.00625 Gm) is indicated.

Hofmann (1941) has described the satisfactory use of a wagon bed like framework of wood, fitted with legs and rollers and filled with sawdust, that portion of the sawdust which is soiled can easily be removed and replaced by fresh, and the whole "bed" can be stirred up daily with a paddle to keep it soft and comfortable. Soft wood sawdust is of course to be chosen and walnut especially avoided because it stains when the patient perspires.

Treatment of Bed Sores.—Once bed sore has developed, its treatment differs from that of other peripheral ulcerations because, even though the area is infected, the application of disinfectant dressings usually aggravates rather than ameliorates conditions, since tissues deprived of nerve supply are easily attacked by chemical as well as bacterial agents. Since its introduction by Latimer, in 1934, the tannic acid heat treatment of such ulcers has been widely and favorably used, for methods see Burns. It is probable that the sulfhydryl-containing compounds, thiocresol, cysteine and thio-glycerol, as used in treatment of varicose ulcers and burns, will prove valuable here also, but as yet results in a large series of cases have not been reported. Warm boric acid compresses are usually employed with results that are none too good, the continuous bath is preferable but its employment is not always feasible. When slough has separated or been curetted away and "stimulant" treatment seems indicated, the time honored therapy is to use on alternate days the N.F. scarlet red ointment and a dressing of equal parts (more or less) of balsam of Peru and castor oil. One would expect sulfhydryl compounds to be especially valuable at this time.

Care of the Bladder.—If there is paralysis of the bladder every effort should be made to prevent overdistention with consequent dribbling and

great danger of maceration of the skin on the one hand and urinary tract infection on the other. But no catheterization, not even the first, should be made under any but the most absolutely aseptic conditions. Catheterization at six hour intervals is the usual procedure, always hoping that automatic emptying of the bladder will be established before the inevitable infection has occurred. When such infection occurs its treatment is that described in Nontuberculous Urinary Tract Infections.

Care of the Bowel—It is customary to give a daily enema, preferably of sodium bicarbonate instead of soapsuds, and to leave the patient on the bed pan for an hour afterward so that all of the slowly returned water may be caught. Some men give such a cathartic as aromatic fluid extract of cascara at night also, but it is possible that this makes the likelihood of abdominal distention somewhat greater, this latter disturbance may cause great annoyance and necessitate administration of 1 cc. of pituitrin hypodermically.

Combating Muscular Spasms—The exceedingly distressing sudden painful spasms of the paralyzed limbs which occur reflexly in some instances when the cord has been severely damaged require the use of large doses of sedatives, see Insomnia.

Massage and Faradization—In recent years there has been a trend away from routine employment of massage in hemiplegia, it is also felt nowadays that electrical stimulation of the muscles with faradic current is not only useless from the standpoint of reestablishment of nervous pathways but is actually harmful in that it goads into further spasm muscles which are already spastic.

Exercises—Practice has moved away from sole dependence on passive movements, indeed, Hobbouse (1936) probably expresses the consensus when he says that in hemiplegia the only passive movements necessary are full movements of joints to maintain mobility and ensure positions of the limbs which will not permit the formation of deformities. On the other hand, everything possible should be done to begin active movements from the very start, before the initial flaccidity has been replaced by spasm. Attempt must be made to stimulate the patient's utmost effort of will as early as possible. Even during the beginning period, when there is likely to be some psychic change, something can be accomplished by persistence, Hobbouse says "irritability in itself provides a stimulus for movement and it is less to be feared than apathy." Metcalf (1934) has recorded that in the return of muscle activity after his own stroke there seemed to be a threshold of resistance which had to be overcome and that this threshold lessened in needed duration in successive trials on any one day and from day to day. Hemianesthesia may impede recovery but it does not seem to necessitate modification of treatment. Expecting a patient to be constantly making efforts to use a paralyzed arm when there is a sound one at his service is asking a great deal, sometimes transient immobilization of the sound one promotes formation of a habit of attempting to use the other. Right hemiplegia in right handed individuals is said to be more likely to be accompanied by aphasia than is left-side involvement, but Hobbouse finds the prospect of motor recovery decidedly better when the right side is affected.

ECLAMPSIA AND HYPEREMESIS GRAVIDARUM

ECLAMPSIA AND HYPEREMESIS GRAVIDARUM

ECLAMPSIA

Eclampsia is a disturbance of pregnancy characterized in the end by convulsions, coma and a high death rate, and nearly always recognizable some time during the last trimester by the appearance of one or all of a triad of prodromal signs—hypertension, albuminuria and edema. The conception that this is a 'toxemia,' or as more frequently stated that it is one of the 'toxemias of pregnancy,' completely lacks support since no one has ever found the alleged toxin or produced more than presumptive evidence of its existence. The pathologic findings, though characteristic in kidney and liver are not such as can be demonstrated in eclampsia alone. Many theories of etiology are current, some quite interesting, some hopelessly weak, all inconclusive. But certain gross facts are crystallizing in clinical consciousness. One is that there are definitely two stages in the malady—preeclampsia and eclampsia—which differ in degree only. Another is that the serious symptoms are those of water retention. And another that if this retention is recognized early enough, much can be done to prevent its progression to the point at which life is threatened. Fortunately no intricate or protracted laboratory studies are necessary, for the diagnosis can be simply arrived at. Headache of sudden onset, visual disturbances, eyeground abnormalities, diminished urinary output, patent edema, nervous irritability—these are helpful but often late manifestations, excessive increase in weight, rise in blood pressure, albuminuria are the cardinal signs to seek and heed. They may appear and disappear independently of one another, but the presence of any one of them is warrant for action. Women do not normally gain more than 20 to 25 pounds during pregnancy, average gain during the last sixteen weeks is 1 pound per week, twice this gain is excessive and suspicious, three times is alarming. A rise in blood pressure from the normal 120/80 or less, to 135/90, or more is suggestive evidence not to be ignored. Albuminuria is definitely not a normal thing.

In the late stage of the attack itself, the patient falls over unconscious and passes from a rigid spasm with opisthotonos, flexed arms, clenched fists, distorted features and dilated pupils into a clonic convulsion during which the whole body twitches very violently, the tongue is protruded and often severely mutilated by the clamping jaws, the eyes are bulging and bloodshot, the face is swollen and cyanosed, blood tinged foam comes from the mouth and the pulse is rapid and pounding. The chest is rigidly fixed. After from thirty seconds to one and one-half or two minutes relaxation takes place and the patient may wake up very exhausted and bewildered or in the most severe cases she remains in coma between spasms and may be delirious.

THERAPY

There are many methods of treating eclampsia, some of them like the famous Stroganoff and its modifications, consisting in little more than heavy narcotic drugging when the convulsions occur, others, like the Rotunda,

and the approach upon the basis of a supposititious hypoglycemia, relying principally upon the free administration of fluids when the convulsions appear, others using hizarra drugs in allegedly more or less "specific" roles and some attempting to combine the most liked features of all the others, thus winning strangely the appellation "conservative." I shall not attempt to present any of these methods here for the reason that it seems to me advisable only to present the more rational one which attempts both to prevent and treat the disturbance by concentrating all attention on combating water retention. The foremost advocates and routinizers of this type of treatment are the group associated with Arnold, at Temple University in Philadelphia, what follows is a condensation of their plan.

Treatment of the Potentially Abnormal—This is the group of patients who are apparently well but who have a history of definite or probable kidney-impairing disease or of previous pregnancy complications possibly involving the kidneys, as well as all with evidences of latent organic disease especially of the kidneys.

(a) Place on a fluid balance basis at earliest recognition of pregnancy 30 to 40 ounces (900–1200 cc.) of fluid intake and output daily.

(b) Five small meals daily with no food or drink except at these three hour intervals.

(c) The diet should be very low in salt and sweets, the former increasing retention and the latter increasing thirst. Since Strauss (1939) finds hypoproteinemia often present in the last trimester of pregnancy, the protein allowance should also be higher than ordinarily taken, for hypoproteinemia is in itself conducive to water retention.

Treatment of the Moderately Preeclamptic—Patients who have some undoubted, even though moderate, indications of approaching danger—overweight, slight or marked edema, hypertension of 30 to 50 points, subjective symptoms still absent or only mild or variable.

(a) Drastically restrict fluids, or withhold altogether if it seems advisable, until twenty-four hour urine output is known, then chart accurately the intake and output daily, or at intervals of a few days, as the case warrants.

(b) Dehydrate more or less moderately with a few daily, or every other day, courses of magnesium sulfate by mouth. 1 or 2 ounces (30–60 cc.) of the saturated solution every hour or two until watery stools are produced.

(c) Meals and dietary ingredients as in (b) and (c) under Treatment of the Potentially Abnormal above, except for the withholding of fluids.

(d) When sufficient dehydration is accomplished, as indicated by reduction in weight and blood pressure, endeavor to maintain water balance as in the preceding potentially abnormal group.

Treatment of the Dangerously Preeclamptic—Those in whom there is already the threat of convulsive seizures, scanty urine, overweight, edema, alarming hypertension (50–100 points), urinary pathology, subjective symptoms—headache, visual disturbances, mental dulness, 'indigestion'—often, but still not invariably, present. The treatment here may necessarily include the following:

(a) If the subjective symptoms indicate great urgency, drain the spinal canal of 40 to 80 cc. of fluid, or, if this is impracticable, withdraw 20 to 30 ounces (600–900 cc.) of blood by venesection.

(b) If the case is less urgent, or after one of the above measures has

been taken, give 50 cc of 50 per cent dextrose solution at four to six hour intervals, alternating two or three times in the intervals with 20 cc of 10 per cent magnesium sulfate solution

(c) The above injections being designed to draw water out of the tissues into the blood stream, magnesium sulfate purging must be employed to get rid of the water through the bowel

(d) If marked improvement is not seen in twelve to twenty four hours repeat the spinal drainage, or repeat it in four to six hours if symptoms continue urgent Withhold fluid until output from bowel and kidneys, and weight reduction indicate effective dehydration

(e) In most instances food and restricted fluid intake may be allowed after twenty four hours if the patient asks for it, but often it is necessary to withhold both for thirty six to forty-eight hours

Treatment of the Convulsive Group—Patients who antepartum or post partum, have reached the convulsive stage or in whom there are signs of impending death without convulsions

(a) Treat as above in all particulars except that the spinal drainage should be repeated at three- to six hour intervals, and that an opiate or a barbiturate may be given to facilitate the first one if absolutely necessary The number of drainages will depend upon their effectiveness in stopping the convulsions restoring consciousness and promoting mental clearing Venesection is rarely necessary in addition Keep the patient warm but seek to avoid the use of hot packs

(b) Arnold says that though some mortality is inevitable in this group one may expect to keep it within 5 per cent As to emptying the uterus he says that by this planned cerebral dehydration they are enabled to "relieve the patient's head rather than her uterus"

Nicodemus (1941) has re introduced oxygen therapy of eclampsia, the matter having been studied by Hofbauer a good many years ago, Nicodemus patients seem to have been benefited but the series was too small to permit the study to be of more than suggestive value

HYPEREMESIS GRAVIDARUM

(Pernicious Vomiting of Pregnancy)

Ordinary morning sickness occurs in about 50 per cent of pregnant women, but the severe form with which we are here concerned is rare It usually begins between the third and sixth week and lasts several weeks to months, the course may be continuous or intermittent The symptoms are loss of appetite, nausea, persistent vomiting, foul breath, emaciation, intolerable thirst, mental aberration, headache, delirium ketonuria, coma and death The pathologic findings in the urine and blood are apparently entirely the result of starvation dehydration and the loss of chlorides through vomiting Many patients recover spontaneously, either quickly or slowly, but a few go on to death, before this final event miscarriage usually occurs and the

stomach suddenly becomes retentive of food. The more severe form of the polyneuritis of pregnancy has generally been associated with hyperemesis gravidarum.

There is not as yet complete agreement regarding the cause of this malady, but the theory that it is due to a metabolic disturbance in the mother resulting in severe carbohydrate deficiency is at present serving very well as a point for therapeutic departure. Ideas regarding vitamin and endocrine deficiencies have gained some recent support. One observer is convinced that the trouble is due to the patient's allergic reaction to the secretion of her own corpus luteum. The older classification of cases into neurotic, toxic, and reflex types, is no longer subscribed to by many observers.

THERAPY

Abortion—Therapeutic abortion will cure all cases if the mother is not already too near death from starvation and exhaustion to stand the operation. But of course this is not advocated as a routine measure by anyone, indeed, when to empty the uterus is an obstetrical point of such nicety that its discussion has no place in a book of this sort. Certainly, under the newer treatment, this radical procedure is being resorted to much less frequently than was formerly the case.

Psychotherapy—The nervous element must not be overlooked. Sometimes the severe symptoms will almost miraculously vanish when an obnoxious person, not infrequently the husband, is entirely banished from the presence of the patient, or she will suddenly recover when threats to employ the actual cautery or some other severe form of therapy are seriously made. A few observers believe that there is a psychopathic factor underlying all cases. Hurst, of England, even goes so far as to say that the artificial termination of pregnancy cures merely by suggestion since the patient naturally expects to recover when what she regards as the cause of her vomiting is taken away.

Carbohydrate Dietary—The theory of carbohydrate deficiency or glycogen deficiency of the liver as the etiologic factor in the nausea and vomiting of pregnancy was extensively developed independently by Titus and Harding and their associates some years ago. The patient is placed on a regimen of at least seven small meals daily, beginning before arising in the morning and ending at bedtime. Carbohydrate foods of all kinds should be chosen, specifying particularly such articles as cooked fruits, dates and raisins, green vegetables, crackers and cookies, honey, sugar, and such desserts as puddings, custards and ices. In addition, Titus recommends the use of a formula as follows: $1\frac{1}{2}$ ounces of lactose and $2\frac{1}{2}$ teaspoonfuls of sodium bicarbonate dissolved in 1 pint of water, this being approximately 10 per cent of lactose and 2 per cent of soda in solution. Two ounces of this is to be taken every two hours.

Dextrose and Saline Intravenously—In severe cases the patient is hospitalized if possible and given sedatives by rectum (such as 10–15 grains of chloral plus 30–45 grains of bromide in 100 cc. of water, night and morning following a cleansing enema) and dextrose intravenously. The method of giving the latter varies. Titus gives two or three daily infusions of 25 per cent solution, 75 Gm. of dextrose for the initial dose, 50 Gm. for the subsequent ones, Dieckmann and Crossen give 1000 cc. of 10 per cent solution three times

dady, Kassebohm and Schreiber give 1000 cc of 5 per cent every six hours, Hendon employs venoclysis—the continuous administration of 5 to 10 per cent solution for as many days as necessary. It is the consensus that insulin administration is not necessary as there is no evidence that this hormone is lacking, however, some men still "cover" the dextrose by giving 1 unit of insulin for each 2 Gm of sugar. Of course if this is done one cannot look upon disappearance of ketonuria as evidence of improvement. Kassebohm and Schreiber (1937) laid down the dictum that response to therapy, if it is to be seen, will occur in forty-eight hours, the chief indications of it being diuresis, slowing of the pulse rate, elevation of blood pressure, and complaint of hunger. The point should not be overlooked that the low blood chlorides need to be replenished, many men give the dextrose in saline solution.

Duodenal Tube Feeding—Van Wyk believes that those who respond slowly or not at all to the intravenous administration of dextrose show a persistent urobilinuria (in the absence of adequate laboratory facilities urobilinuria may be assumed to be present when the urine has a characteristic orange red color). This he interprets as evidence of a gravely disordered liver function which calls for the administration through the duodenal tube of additional calories. The method is to give 3 ounces (90 cc) of skimmed milk and the same quantity of 10 per cent dextrose solution every two hours throughout the twenty four, this gives the patient 750 additional calories as well as 2000 cc more water (see also below).

Vitamin Therapy—Luikart (1933) believed that the exclusive employment of dextrose and large amounts of fluid may wash out considerable vitamin B complex, which may indeed have been lowered by the pregnancy itself. He added orange juice, broth, lactic acid milk, and cream to the dextrose solution given through the duodenal tube. In the years since, a number of men have stated their belief that supplementary vitamin therapy is advisable, Lund (1940) has recently reported 2 cases in which there seemed little doubt of the associated avitaminosis. Indicated in these cases are riboflavin, nicotinic acid and thiamine, of the B complex, and ascorbic acid (C), all of which can be given parenterally, as soon as progress permits. A and D may be added by mouth.

Adrenal Cortex—This is one of the newer things in the treatment of a condition whose etiology is unknown. Freeman *et al* (1937) reported excellent results in 16 cases in which the combination of dextrose and vitamin forcing was supplemented by the use of adrenal cortex. More recently, Kotz and Kaufman (1940), using the more refined and concentrated product now available, have treated 50 cases, the dosage being 1 capsule three times daily before meals, sometimes supplemented by a daily subcutaneous injection of 1 cc. The latter observers found it difficult to evaluate the therapeutic effects of the agent but thought that most of the patients were markedly benefited.

Progestin—Finch (1940) has used injections of progestin (natural), the corpus luteum hormone, in attempting to "desensitize" 51 patients, he says 91 per cent of the series were relieved of symptoms. Dosage began usually with $\frac{1}{2}$ international unit of progestin in oil intramuscularly, 1 unit being given one day later, treatment then followed at forty-eight- to seventy-two-hour intervals until vomiting ceased, increasing the dose gradually to 3 or 4 units if necessary, when vomiting ceased the top dosage was somewhat reduced and given at five- to seven-day intervals two or three times more.

Vomiting was said to have stopped in an average of about five days and nausea in eight days, the longest persistence of these two symptoms being nine and nineteen days respectively

Nitrites—Because of the alleged close relationship between pregnancy and the origin of biliary disease and because spasm of the second portion of the duodenum produced by morphine was accompanied in some cases by nausea or biliary colic, McGowan *et al* (1938) studied the duodenum in 2 patients suffering from hyperemesis gravidarum. In each case spasm of the second portion was found and readily relaxed by inhalation of amyl nitrite. At the time of writing they had successfully treated 12 cases by the use of nitroglycerin, the patient is instructed to lie down for a little while after each meal, during which time she allows a hypodermic tablet of $\frac{1}{100}$ grain (0.0006 Gm) to dissolve under the tongue.

GENTO-URINARY INFECTIONS AND STONE

GENITO-URINARY INFECTIONS AND STONE

GONORRHEA

Gonorrhea in adults is contracted during the act of sexual intercourse and in the male appears primarily as an infection of the anterior portion of the urethra, the early involvement of the urethral glands, however, playing an important part in maintaining the infection. The average incubation period is three to five days. Profuse purulent discharge is the rule and is usually accompanied by painful micturition. Edema of the parts is not often sufficient to prevent free voiding, but infiltration of the corpus spongiosum is sometimes sufficient in degree to destroy the elasticity of the urethra so that on erection the penis curves downward, giving rise to the very painful symptom known as chordee. When the infection spreads behind the sphincter, which occurs in the majority of cases between the second and fourth weeks, the so-called "posterior" urethritis is established. In its train often come prostatitis, epididymitis, and seminal vesiculitis. Gonorrhea in women is usually indicated subjectively in the beginning by a feeling of unusual dryness and discomfort about the genitalia; this is soon followed by a burning sensation and the appearance of a discharge, which is accompanied by smarting on urination and increase in frequency. The infection is limited in its distribution, for it is only in the very young and the very old when the cornified layer of epithelium has not yet formed or has disappeared, that the vagina itself is involved early. The primary points of localization are in the urethra, the urethral (Skene's) glands, the vulvovaginal (Bartholin's) glands and the endocervix. The vaginal walls and the structures around the vaginal orifice become hot and rough and tender but they are not in themselves infected by the gonococcus in the beginning. The discomfort of acute gonorrhea in women usually passes away very quickly, but the process nearly always becomes chronic, just as in the male. The natural barriers against the upward extension of the infection into the uterus and the adnexa are very great, but once this extension takes place the resultant endometritis, salpingitis, etc., are serious affairs indeed. Noeggerath, in 1872 was probably the first to lay stress upon the importance of latent gonorrhea in the female.

Gonorrhea is believed to outrank in incidence a number of the common infectious diseases in children, but its true incidence is unknown. Its greatest frequency is in girls up to the age of five years, but it may occur at any age up to puberty. The disease is contracted indirectly from infected adults through such media as clothing, bedclothing, towels, diapers, bath sponges, and innumerable other household materials. Perhaps the common toilet seat is the disseminator in some instances, in many others it is very likely that the disease is passed from child to child during precocious manipulation of the genitals. Rape is an infrequent cause. Some observers believe the cervix to be so frequently involved that the disease would more aptly be styled "cervicovaginitis." The symptoms are painful urination and pain on walking, pronounced redness and edema of the external genitalia, coapted

labia majora, and a thin watery secretion which soon develops into a thick yellow, offensive discharge. The gonococcus can be demonstrated in about 50 per cent of cases, rectal cultures are also often positive but clinical proctitis seems to be very rare. In the majority of instances the condition undergoes spontaneous cure in about three months (Cohn *et al*, 1940), but in many children the infection causes considerable discomfort and lasts as long as six months, occasionally for several years. The impression that the disease terminates invariably at puberty is a common one, but Benson and Steer (1937) record 2 girls in their clinic still showing positive smears though menstruating six and eight months respectively at the time of report. Complications are fortunately very rare in these cases in childhood.

Gonorrheal arthritis first clearly described by Brande, in 1854, and endocarditis are serious complications, which occur of course only after the organism has entered the blood stream in considerable numbers. If the gonococcus is conveyed to the conjunctiva by the hands or other contaminated object an acute infection often resulting in blindness follows that this catastrophe does not occur with greater frequency than is the case is solely due to the fortunate fact that the organism perishes very quickly outside the body, though cases of its survival on damp towels for twenty four and dry towels for twelve hours are on record (Dobszay, 1933). In most cases of gonorrhea there are few systemic symptoms beyond malaise and a slight headache, though the leukocytosis is indicative of a general reaction. Psychic disturbances are often quite pronounced, but they are probably for the most part engendered by the patient's fear that what he looks upon as his moral dereliction will be discovered.

Gonorrhea would seem to be as old as man, for very many of the ancient writings that have come down to us, both religious and secular, contain references to this "flow of semen" disease. However, so far as we now know the true nature of the discharge and the recognition of the infectious and venereal nature of the malady were not recorded until quite late in the Middle Ages. Fernel in the sixteenth century, seems to have differentiated gonorrhea and syphilis, apparently the disease was very common at that time, but in John Hunter's day (1728-1793) we find the two diseases again confused, Ricord in 1838 finally established the separate entities. In 1879 Neisser discovered the causative organism, now known as *Neisseria gonorrhoeae*. Regarding the present incidence of the disease, it can only be said that it is very prevalent all over the world, but whether it is on the increase or decrease cannot be stated with any positiveness, though the drafted rejections in World War II as compared with World War I indicate that the incidence has declined in the United States.

THERAPY

Sulfonamides — The introduction of these drugs has completely revolutionized the treatment of gonorrhea. In one sentence in Parsons' (1941) authoritative report of the disease in the US Navy in 1941 this change is succinctly and unforgettably expressed "The old familiar scenes of crowds of men lining up at the trough with their argyrol syringes and permanganate irrigating jars have vanished." Sulfanilamide was not entirely satisfactory, but both sulfapyridine and sulfathiazole have proved highly effective, the latter being usually preferred because of lower toxicity and perhaps greater

efficacy. It would seem that in all types of gonorrhea—in men or in women in adults or in children, in acute cases or in chronic cases—these drugs are able to effect cure in nearly all instances, the proportion of cures varying in the different reports from 85 to 96 per cent, with the average certainly well over 90 per cent. The amount and type of treatment which the patient had preceding the use of sulfathiazole apparently does not affect the outcome. Complications of all sorts respond as well as the primary infections and in acute cases which are uncomplicated when therapy is begun complications practically never appear. In all types discharge ceases upon the average in three days and smears become negative at the same time. The length of treatment courses varies somewhat because practice has not yet become standardized, some men using a five-day course, some seven, ten or twelve days. A number of observers agree with Uhle *et al* (1941) of the Philadelphia General Hospital who feel that in cases refractory to a single course of treatment it is best to stop awhile—the usual interval is ten to fourteen days—and then give another course rather than treat continuously for a prolonged period. Moffett (1940) thinks this is also good practice in vulvovaginitis cases in children. Fletcher *et al* (1941), who had the opportunity of treating a considerable number of prostitutes under conditions of exceptionally good control, had their women take a second course of the drug during the subsequent menstrual period unless menstruation occurred while the first course was being taken, the thought being that perhaps menstruation exacerbates the infection.

This new chemotherapy has outmoded the old provocative tests (failure of discharge to occur following indulgence in alcohol or sexual excitement, massaging over a sounded urethra, or the presence of gonococci in the discharge provoked by the injection of 1 per cent silver nitrate) as criteria of cure since patients will not respond to them after chemotherapy though smears and culture studies may still give positive results. New criteria of cure have therefore to be devised. For the male, Uhle *et al* (1941) would have at least three sterile cultures of the prostatic fluid obtained at intervals of five to seven days following the cessation of discharge. In their studies with sulfathiazole they found the average time elapsing between the disappearance of symptoms and the last positive culture to be seventeen days, the extremes being three and fifty-three days. Their advice to the physician unable to have this routine cultural work done is that he treat his patient to or even beyond this average seventeen-day period. The Committee on Chemotherapy of the National Research Council, advising the U.S. Army in its Circular Letter No. 18 (J.A.M.A., May 24, 1941), requires eight consecutive weekly negative smears of prostatic secretion, the first smear to be made fourteen to twenty days after the start of treatment if all symptoms have disappeared. In their women Fletcher *et al* (1941) were able to do weekly smears and cultures for fifteen weeks but only 44 per cent were positive at three weeks and none at six weeks. In children Rice *et al* (1941) propose the following criteria of cure: a clinically normal condition and at least seven consecutive negative cultures during sixteen weeks.

It would appear from the work of Kendell *et al* (1941), Rose *et al* (1941), and Frautman (1942) that a considerable proportion of the small number of patients who are refractory to the sulfonamides will respond to a combination of sulfonamide and artificial fever (hyperthermia) therapy.

Sulfonamide Toxicity—See the separate chapter on this subject at the end of the book.

Sulfathiazole Dosage—It should be stated that sulfathiazole and sulfapyridine dosage are the same but since the former has replaced the latter drug because of its lower toxicity I shall discuss only sulfathiazole dosage. As a matter of fact a wide range of dosage seems still to be in use for in papers published during 1941 I find recommendations of daily dosage for adults of from 30 to 75 grains (2 to 5 Gm). It seems however that one can take as probably the most satisfactory guide the plan recommended by a special committee of the National Research Council to the heads of the armed forces and the public health service (Circular Letter No. 18 JAMA May 24 1941). According to this plan the adult with gonorrhea is to receive

1st day	sulfathiazole 7½ grains (0.5 Gm) every three hours for 6 doses
2nd to 9th days	five " " 4
10th day	If patient is, and has been since the 5th day symptom free stop all dosage

It is an integral part of the above plan to switch to sulfapyridine on the fifth day if the discharge has not ceased by that time under sulfathiazole. Of course it is recognized that the time schedule necessitated by employment of this plan (dosage must begin at 6 A.M. and last until 9 P.M.) is perhaps a bit rigorous for private practice. A somewhat easier plan is that recently reported by Mahoney *et al.* (1941) as a result of the study of various dosage schemes in 360 patients give 7½ grains (0.5 Gm) of sulfathiazole at 8 A.M. 12 Noon 4 P.M. and 8 P.M. daily for ten days.

In vulvovaginitis of infants and young girls a plan of treatment such as that recently employed with excellent effect by Lewis (1941) in 80 cases seems to be about typical. Sulfathiazole in 4 divided doses at four hour intervals for seven to ten days the total dose per day not to exceed 30 grains (2 Gm) and being based upon a calculation of ½ grain (0.03 Gm) per pound body weight.

General Measures—Still today as before the advent of chemotherapy the taking of alcohol sexual indulgence or excitement and heavy manual labor retard and may even prevent recovery. Diet is of no importance nor is fluid regulation. As much rest as is possible consistently with the necessary daily activities should be obtained during the period of active treatment.

Local Treatment in the Male—It is now the consensus that nothing is gained by local treatment combined with the use of sulfathiazole by mouth. However in the small proportion of cases in which response to sulfathiazole is not satisfactory something must still be done. I set down here the plan for local treatment of the American Neisserian Medical Society as published in slightly altered form by Pelouze (1940).

Anterior Urethritis—1 After urination the anterior urethra is cleansed with 1:10,000 to 1:5,000 solution of potassium permanganate either by low pressure irrigations or by gentle band injections by means of a syringe.

2 By means of a bulb syringe not more than 6 cc. of a 5 to 10 per cent solution of mild protein silver (U.S.P.) or from 0.25 to 0.5 per cent strong protein silver (U.S.P.) is injected into the urethra and kept there for five minutes. (The weaker strengths are better.)

3 Such treatments are carried out daily until there is no urethral discharge and then every other day. If the latter interval proves too long, as evidenced by the recurrence of discharge, daily treatments should be resumed for a few days and the interval again increased. Later, when safe to do so the interval is increased to every third day.

4 If the patient cannot visit the physician frequently enough for this regimen to be carried out, a one-eighth ounce glass syringe and 0.25 or 0.5 per cent solution of strong protein silver (U.S.P.) is ordered with instructions to use it twice a day.

5 It is safest not to try the ordinary tests of cure for patients under either of these two plans of treatment before the end of the fifth week in the most favorable of cases. (This does not apply to the real or seeming sulfonamide successes.)

6 Every effort should be made to obtain the patient's cooperation and no local treatment should be placed in his hands without the most explicit instructions as to their proper use.

7 Such patients should have described to them the symptoms of posterior urethral involvement and be told to stop local treatment and present themselves at the physician's office if they occur.

Posterior Urethral Involvement—1 Local urethral treatments should be stopped until the acute symptoms subside.

2 Acute symptoms can be controlled with sedatives and hot hip baths.

3 After vesical comfort has been regained entirely, low pressure intravesical irrigations of potassium permanganate solution should be given at intervals of two or three days.

4 Prostatic or seminal vesicular manipulations should be avoided until the second glass of urine is clear and the first is almost clear.

5 One should start massage with the very gentlest prostatic strokings and if it causes a return of urethral discharge one should wait a week before trying again. If it causes no such recrudescences of symptoms it should be repeated at intervals of from three to four days, the pressure being gradually increased at subsequent visits but never reaching a point of roughness.

6 The massages should be continued at these intervals until the prostatic secretion is free of pus.

7 During the first month or six weeks of prostatic massage it is well to carry out a preliminary intravesical irrigation, some of the solution being left in the bladder to be voided after the massage. If after this time the irrigations are discontinued, there rarely will be any shreds in the urine when the patient is ready for dismissal.

Local Treatment in the Female—Local treatment has been shown to be unnecessary and not helpful during the treatment with sulfathiazole. The local measures which are indicated in the small proportion of patients who do not respond to chemotherapy are gynecologic matters whose discussion has no place in a book of this nature.

Local Treatment in Vulvovaginitis—None of the local treatments for this condition had ever been established upon a satisfactory basis now that has all been superseded it would seem by the systemic employment of the sulfonamides.

Estrogen Therapy in Vulvovaginitis—This too has been superseded by the sulfonamides.

Complications in the Male—It is now rare indeed that complications occur in the case that is promptly treated with sulfathiazole. When they are present at the start of treatment and fail to yield to the drug it is usually advisable to have specialist consultation or to refer the case—something should be left to the venereologists! The minor matters of chordee and phimosis still sometimes seen usually respond to the soaking of the penis in hot water. Of the treatment of paraphimosis Pelouze (1936) writes 'The foreskin should be replaced as early as possible to prevent induration and ulceration at the point of greatest constriction. In order to do this the glans penis should be grasped by the gloved fingers of one hand, while the other hand is used to encircle the swollen, misplaced prepuce. Gentle, continuous pressure should be made upon both structures until about all of the swelling is gone. The parts then usually are easy to place in their normal positions. To prevent subsequent retraction it is well to pass a strip of adhesive plaster along one side of the penis over part of the preputial opening in such a way as to make it smaller but not occlude it, and then down along the other side of the penile shaft. This should be left on for several days. In the presence of neglected paraphimosis with much induration it occasionally is necessary to incise the constricting band on the dorsum of the penis. If ulceration has taken place it is wise to attempt to sterilize the surface by the application of tincture of iodine before incision of the constriction. Ulcerations of the glans penis from prolonged penile constriction usually heal promptly upon the use of an antiseptic dusting powder. Before this is used, however, a dark field study of the ulcer fluid should be carried out.'

Complications in the Female—Such of these as do not yield to sulfathiazole are gynecologic affairs entirely outside the province of this book.

SYPHILIS

(See under *Infectious Diseases*)

CHANCROID

Chancroid is next to gonorrhea, probably the commonest of the venereal diseases in the male. It would seem that the organism is able to maintain a saprophytic existence in the female, for the ulcerations are comparatively rare in women, even in those who are known to have been the direct infecting source of men. The bacillus of Ducrey is the causative agent but is very difficult to find. Though the intradermal test of Ito is nowadays available for use in doubtful cases diagnosis is usually still made upon clinical findings, having always uppermost in mind the necessity to make thorough dark field examination to eliminate the possibility of the lesion being syphilitic in origin. The incubation period is one to several days at the end of which time there

develop one or more small ulcers with a dirty base, these usually spread rapidly, by contiguity and continuity, discharging more or less pus, bleeding freely, and causing destruction of tissue. The most frequent site of the initial lesion is the coronary sulcus, but the process may begin at any point on the penis, extragenital lesions are extremely rare. As the ulcerations spread, there is much pain and inflammation and swelling of the affected parts. In the individual with a long foreskin there often occur varying stages of phimosis and paraphimosis. In about 50 per cent of the cases, especially those remaining ambulatory, the draining lymph glands are affected, giving rise to the condition known as bubo.

John Hunter (1728-1793) clearly distinguished between true syphilitic chancre and this false, "soft" chancre. Ducrey discovered the causative *Hemophilus ducreyi* in 1889.

THERAPY

Sulfonamides—In the last edition of this book I included several pages of alternative local treatments of this most resistant condition which was of course indicative of the fact that none of the treatments was effective in a very large proportion of cases. Now I have eliminated all of these measures because experience in recent years has shown the systemic employment of sulfonamides to be superior to local treatment at all stages of the infection—ulcer, bubo ruptured or bubo unruptured. The simple local treatment nowadays employed (see below) is of an entirely new sort. Average experience seems to be that healing occurs in about two weeks: witness Hutchinson's (1938) fifteen-day course in 11 sulfonamide treated cases, forty six days in 12 vaccine treated cases, and forty six days in 12 locally treated cases. Schwartz and Freeman's (1940) 37 sulfonamide cases healed in fifteen days as against thirty two days for locally treated cases, etc.

Dosage—At the time of this writing, early 1942, sulfanilamide is still the preferred drug. The dosage recommended to the armed forces and the Public Health Services in Circular Letter No. 18 (J. A. M. A., May 24, 1941) of the special committee of the National Research Council follows: 45 grains (3 Gm.) daily, in divided doses at four hour intervals, for five days; thereafter 30 grains (2 Gm.) in divided doses daily for an additional nine days.

There is no reason why sulfonamides should not be administered while arphenamines are being given if this is imperatively necessary. Sulfonamide toxicity is discussed in a separate chapter at the end of the book.

Local Treatment—The Committee on Chemotherapy of the National Research Council, advising the Army, Navy and Public Health Services in its Circular Letter No. 18 (J. A. M. A., May 24, 1941), recommends the following to supplement the systemic employment of the sulfonamides: (a) Cleanse accessible lesions with soap and water, dry, and cover with powdered sulfanilamide and a dry dressing, repeat daily. (b) If there is tight phimosis and underlying ulcerative lesions irrigate the phimotic preputial cavity twice daily with 1:5000 potassium permanganate solution. Kornblith *et al* (1941) have found sulfathiazole powder also effective for local application. For treatment of paraphimosis, see Gonorrhea.

Buboes which do not subside promptly under systemic sulfonamide therapy may be aspirated through a small incision and the cavity packed with sulfanilamide powder.

BALANITIS

Erosive balanitis is an infectious venereal disease due to the symbiosis of a fusiform bacillus and a spirochete both of which are anaerobic and structurally resemble those found in Vincent's angina. It is a fairly uncommon affection even in large venereal clinics. Red superficial lesions with a necrotic border appear on the glans or foreskin and enlarge peripherally and become confluent to form circinate lesions with polycyclic borders. They do not give rise to bubo though there is sometimes an inguinal adenitis. The thin yellow abundant pus is very foul smelling. Phimosis is an early and annoying complication. There are usually no constitutional symptoms but in rare instances gangrenous extension suddenly begins to take place very rapidly the glans and prepuce and in some instances the entire shaft of the penis being destroyed in a surprisingly short time. In this gangrenous form of the disease there are always grave constitutional symptoms and death is frequent.

THERAPY

The key to the treatment of this disease lies in the fact that the organism does not flourish when exposed to oxygen. The usual practice is to open the prepuce by a dorsal slit so that the glans is completely uncovered and then to keep the parts clean either by wet dressings or by continuous irrigation with 2 per cent solution of hydrogen peroxide. Most cases of the erosive type heal rapidly under this treatment especially if the parts are kept exposed to air at all times when the oxidizing agent is not being used.

The use of neoarsphenamine intravenously as in the treatment of syphilis is said to hasten recovery. In cases of other genito-urinary lesions complicated by a superimposed fusospirochlosis Greenblatt and Wright (1936) have obtained good results from applying liberally to the lesions once or twice daily after preliminary thorough cleansing with sodium perborate solution the following mixture: 6 Gm neoarsphenamine 30 cc glycerin 30 cc cod liver oil.

Sutton has described the use of subcutaneous injections of oxygen in a case of the gangrenous type as follows: When I first saw the patient five days after the onset of the disease almost the entire dorsum of the penis was involved the skin and subcutaneous tissues being soft and gangrenous. During the following thirty six hours the infection continued to spread despite the frequent and liberal use of hydrogen peroxide by irrigation and by moist packs. At this time subcutaneous injections of oxygen were begun by means of an ordinary hypodermic needle connected to an oxygen tank through a small rubber tube and repeated every four hours. The normal tissue surrounding the affected area was first treated the flow of gas being regulated by means of a small screw clamp encircling the outlet tube. Afterward the involved structures also were thoroughly impregnated with the gas. Within six hours the progress of the disease was checked and within twelve hours it was completely under control. Shortly afterward the slough began to separate and recovery aside from the deformity resulting from loss of tissue was prompt and uneventful.

PROPHYLAXIS OF VENEREAL DISEASES

We know very little of the value of venereal prophylactic measures in civilian life, such knowledge as we have being derived entirely from army and navy studies. It was the feeling among most of those who had to do with these matters during World War I that prophylaxis was successful in bringing about a marked reduction in the incidence of all three of the principal diseases, syphilis, chancroid and gonorrhea. Moore of Johns Hopkins Hospital, who was the inspector of the prophylactic stations in Paris and had 25 of the 72 under his immediate control, made a statistical study of the results and believed that the man who failed to take the treatment was more than seven times as likely to contract disease as the man who did take it. He found that the earlier it was applied the more effective it was, the difference in its value when applied six or seven hours, for example, after exposure rather than one hour being very great, but he thought it still worth while giving, especially for protection against syphilis, even as late as twelve hours. But this enthusiasm of Moore was specifically for one method only, namely, the presumably expert application of the prophylactic measures by trained soldier attendants in the prophylactic stations which it was compulsory for soldiers to attend who had exposed themselves to infection. The prophylactic packet has been almost universally declared a failure, it has also been shown that the application of prophylactic measures by the soldier himself in the station is of no worth. I shall describe Moore's method, merely remarking in passing that Harrison's (1931) review of the matter contributed by request to the *Lancet*, did not exhibit any general faith in its efficacy, and that Boyden (1936) has shown that it has failed on the Asiatic Station of the U.S. Fleet—Parsons (1941) states that it is currently employed in the Navy as a sort of superfluous ritual, much like 'the use of the finger bowl at the conclusion of a meal'. It is significant also that the joint committee appointed by the American Social Hygiene Association and the U.S.P.H.S., reporting upon their study of the matter at the end of 1940, stated their opinion to be that (a) chemical or mechanical prophylaxis is supplementary to and not a substitute for prophylaxis by educational measures which employ ethical and religious motives, (b) the preferred method of prophylaxis, the above measures having failed to prevent exposure in an individual case, is the use of a condom of good quality, (c) a condom not having been used, such measures are to be employed as are described below.

Method (for the Male)—As a first step the patient is instructed to urinate and then, being provided with a pint of warm water in a basin and a gauze wipe, he washes thoroughly, while the attendant drops liquid soap on the penis. The next step is the injection of 1 drachm (4 cc.) of 2 per cent protargol or 10 per cent argyrol solution into the urethra by the attendant. The patient then holds the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus so that all parts of the urethra are kept in contact with the solution. At the end of five minutes the solution is allowed to escape without pressure so that a few drops remain. One-half drachm (2 Gm.) of 33½ per cent calomel ointment is next rubbed thoroughly by the patient, under the observation of the attendant, into all parts of the penis for five minutes special attention being paid to the retracted prepuce, the frenum and the glans. Finally the penis is

wrapped in toilet paper to protect the clothes and the patient instructed not to urinate for four or five hours

Method (for the Female)—Moore's method "Have the patient urinate Place the patient in the lithotomy position Wash the genitals and adjacent parts with soap and water Give a douche of 2 quarts of sterile water, temperature 100° F., followed by 2 quarts of 1:2000 mercuric chloride solution and wash external parts with the latter Dry the vagina and vulva by sponging Swab the entire vagina through a speculum, with a 2 per cent protargol solution, or 10 per cent argyrol solution, freshly made, reach every fold and especially the posterior vault and external os Swab the entire vulva in the same way, reaching every recess and endeavoring to facilitate the entrance of the solution into the openings of Skene's ducts and Bartholin's glands Inject enough of the same solution into the urethra to distend it moderately and let the patient hold her finger (in a rubber glove) against the meatus to retain the solution for from three to five minutes

'Douché the vagina and vulva with a small amount of sterile water and sponge dry with gauze Apply calomel ointment to the cervix, vagina, vulva and adjacent parts, rubbing thoroughly into the recesses and folds of the mucous membranes and skin and taking at least ten minutes for the operation Do not use more than 4 Gm (1 drachm) of calomel ointment in the vagina Cover the external parts with oiled silk or waxed paper securely and instruct the patient to allow ointment to remain for several hours before washing the parts

Prophylactic Use of Arsenicals or Bismuth—There is now unanimous agreement among students of this subject that the administration of a few doses of an organic arsenical or a bismuth preparation after a suspicious exposure is not a desirable thing for the reason that it can prevent the development of the primary sore but not the infection, thus leaving the patient, as Harrison expresses it, "in a fool's paradise" With the results of treatment of seronegative primary syphilis being what they are today, the approved line of action is to wait for the appearance of a chancre before proceeding to institute treatment

GRANULOMA INGUINALE

(*Granuloma Venereum*)

Granuloma inguinale is a chronic infectious, ulcerative process, usually involving the genitalia or neighboring parts, and showing no tendency toward spontaneous healing Most of the cases are seen in young adult Negroes with perhaps an even distribution between the sexes The disease is probably not venereal since wives or husbands often are not affected though continuing to cohabit when one is infected The process begins as a small moist papule which rapidly ulcerates thereafter, invasion of the surrounding tissues by the elevated, reddish, often shiny, delicately skinned granulomatous proliferations is gradual and eccentric Where moist the lesions are superficially ulcerated but where dry they are cracked Aden

opathy is characteristically absent, though the occurrence of elephantiasis of the genitalia, or of a leg, signifies involvement of the lymph channels. Except for the presence of the lesions and a slight itching or burning sensation, the patients experience little discomfort. The discharge from the ulcerating areas is held by some observers to have a quite characteristic odor, but having once seen the entire staff of a reputable hospital led temporarily away from their correct clinical diagnosis of epithelioma by the asseveration of an expert in this disease that he "smelled granuloma in the ward," I am extremely doubtful of the value of this diagnostic sign. Wilson's (1930) study of a small series indicated rapid progression and a tendency toward stillbirth in cases complicating pregnancy. Arnell and Potekin (1940) state that 38 cases of granuloma inguinale of the cervix had been observed at Charity Hospital in New Orleans in the ten years preceding their report. Crane and Kimball (1940) describe a case in which there was involvement of the rectum and colon; in Becker's (1939) case autopsy showed involvement of the intestinal tract and the ribs. Extragenital skin lesions have been occasionally reported.

The disease was recognized by MacLeod, in India, in 1882, but it was first accurately described by Conyers and Daniels, in British Guiana, in 1896. In 1905, Donovan, in India, first described the organism now believed to be causative, but strange to say, it is not definitely known as yet whether this organism is a protozoan or a true bacterium. It is found in all parts of the lesions, but especially in the deeper areas, where all other organisms are absent. The characteristic histologic picture described by Pund and Greenblatt in 1937 now seems to be recognized by other workers as well. Alexander and Schoch (1940) find the use of Giemsa stain necessary to bring out the pathognomonic giant-cell. The geographic distribution of the disease is very wide, including India, southern China, Australia, West Africa, the East and West Indies, and parts of North, Central and South America. Its widespread presence in the United States is now generally recognized though undoubtedly it is more prevalent in the South than elsewhere.

THERAPY

Tartar Emetic—Antimony and potassium tartrate was first used in the treatment of this disease by Aragão and Vianna of Brazil. In cases which respond satisfactorily the lesions involute progressively and the Donovan bodies disappear. It is usual to use a 1 per cent solution beginning with 2 cc intravenously and increasing 1 to 2 cc at a time until 10 to 12 cc are being given at a dose. The injections are given at intervals of two to three days. Ten or 12 injections may clear the lesions sufficiently that it is difficult to hold the patient for further treatment, but it is the consensus that to avoid relapse weekly injections should be given for two or three months after entire healing, followed by 2 injections monthly for four months. Robinson (1939) says that good results are to be expected only in early cases, which is a somewhat more conservative view of antimony therapy than he formerly took. Many men have become similarly skeptical in recent years. Arnell and Potekin (1940) say that tartar emetic is still the best drug but, like some others, they now like to excise large growths with electrocautery before beginning the therapy. Response to the drug seems to be much less complete when sinusitis is present as a complication.

Antimony Sodium Thioglycollate and Thioglycollamide—Raadal (1931) presented evidence that the first of these drugs might prove to be preferable to tartar emetic in that it is less toxic and apparently more effective. Several of his patients who were intolerant to tartar emetic took the new drug without reactions. The dose is 0.05 to 0.1 Gm. dissolved in 10 to 20 cc. of sterile water and given intramuscularly every third or fourth day until 15 to 25 injections have been given. The number of cases thus treated is as yet not very large. Hazen *et al.* (1932) used antimony thioglycollamide with "striking therapeutic response" in 3 cases. Senear and Cornbleet (1932), and Patch and Blew (1930) also used the drug successfully, though I believe the thioglycollate is usually considered to be less toxic. No recent reports of the use of these agents have come to my attention, though both remain Council accepted.

Fuadin—Williamson (1933) and his associates reported enthusiastically upon their success with this new trivalent compound of antimony and sodium in 14 cases. Their treatment consisted of 12 intramuscular injections on alternate days of a 7 per cent solution, the first injection was of 1.5 cc., the second of 3.5 cc. and the subsequent injections each of 5 cc. No reactions considered dangerous were observed though 3 patients experienced generalized subacute joint pains after certain of the injections persisting at times long enough to cause postponement of the subsequent injection one day. More recently, Arnell and Potekin (1940) say they find tartar emetic the better drug. Goldblatt (1939) finds the results with both fuadin and tartar emetic 'rather disappointing', Greenblatt (1939) says that many cases respond well to either of these drugs in the beginning but then have a recurrence.

Sulfonamides—These agents have not made a place for themselves in the treatment of granuloma inguinale.

LYMPHOGRANULOMA VENEREUM

(*Lymphogranuloma Inguinale, Climatic Bubo, Venereal Lymphogranuloma*)

This is a specific venereal disease which always follows sexual exposure and therefore is seen with extreme rarity in children. Men predominate among the victims of the inguinal form, but the anorectal localization is seen often enough in women (occasionally in men also) probably to equalize the sex distribution. Elephantiasis of the pudenda is also a manifestation of this disease. The initial small lesion on the external genitalia is not often seen, but it is known that the incubation period after exposure is between three days and three weeks. Usually the glands of only one side are involved but bilateral cases are on record, there is gradual progression until a fist size mass bound together by periaadenitis is formed, and then breakdown and fistula formation take place, a thin seropurulent fluid drains for weeks and months. Occasionally, however, no breakdown occurs. The rectal cases usually lead to serious stricture interfering with defecation, complicated with infection of the rectum, anus and perirectal tissues, the most dreaded com-

plication is rectovaginal fistula. The study of Wilson and Hesseltine (1942) indicates the possible hazard of mismanaged labor if the pelvis is obstructed. Constitutional symptoms of varying severity are observed in the majority of cases in the acute stage. Remote lesions, suggesting a generalized systemic infection have been described, but in their authoritative review D'Aunoy and von Haam (1939) take the position that in view of the rarity of remote lesions and the frequency of localized genital lesions it may be assumed that in most instances disseminated virus is soon destroyed. That the causative organism is a filtrable virus was shown by Hellerstrom and Wassen, in 1913, it is transmissible to several laboratory animals. The antigen diagnostic test introduced by Frei in 1925 has greatly stimulated the study of this disease, it is now recognized, however, that the test is positive in some instances in which there are no clinical evidences of infection. Paulson (1939) feels that his special "bowel" antigen is of value in the differential diagnosis of confusing intestinal involvements. Several successful cultivations of the virus have been reported but none as yet have been universally accepted.

It is now thought that John Hunter treated cases of lymphogranuloma inguinale because of some descriptions in his 'Treatise on Venereal Diseases,' published in 1786, many men later described similar clinical pictures, but the individuality of the disease and its probable venereal nature were only truly pointed out by Durand, Nicholas and Favre, in 1913. Originally considered to be only tropical in its distribution, it is now recognized as occurring practically everywhere, though the greatest incidence seems to be in the warm, humid lands, however, Schutte and Lubitz (1940) have recently found 93 cases in the proctologic clinic of our own school here in Milwaukee.

THERAPY

As in the therapeutic approach to all relatively "new" diseases, a host of remedial agents has been tried all the "specifics" (quinine arsphenamines, antimonials, sulfonamides), diathermy, local application of a filtrate from the infected glands, x-ray, radium, foreign protein and other fever therapy, surgical extirpation of the glands. Success with none of these measures has been consistent. In 1939, D'Aunoy and von Haam reported that their best success had been with antimonials. There have recently been several reports of the satisfactory use of sulfonamides, particularly in the early stages, but taking into account the tendency to spontaneous recovery in this disease some of the results do not seem particularly brilliant—for example, 14 of Schramberg's (1941) 16 patients experienced early symptomatic relief, but 7 of them still showed unresolved lesions from one hundred two to three hundred twenty-five days after treatment was begun. Hawking's (1940) series comprised only 4 treated cases with 11 controls, but he saw no evidences that recovery occurred more quickly in the treated cases. However, Stein (1940) cured all of his series of 32 cases (bubonic lesions only) with sulfanilamide in five days to four and one half weeks except for two sinuses which drained for about three months. And Earle (1939) reported uniformly good results with sulfapyridine in 23 cases of all types except elephantiasis of the vulva and rectal stricture in the male. Palmer *et al* (1942) feel that both sulfanilamide and sulfamylguanidine therapy are of definite value, particularly in cases without stricture formation, but that prolonged administration of the drug may be necessary.

Wien and Perlstein (1937) had some success with the use of Frei antigen in early cases, Howard and Strauss (1935) also cautiously mentioned their favorable impression in a small series of cases. 0.1 cc. of the antigen is injected intradermally biweekly until symptoms are alleviated, weekly thereafter. Kornblith (1939) has given the antigen intravenously in 207 cases, the injections of 0.5 cc. being given on alternate days three times weekly. In most instances the treatments were continued through many months, in some instances several years. It is said that the best results were obtained in the group with glandular involvement only, with symptomatic relief in some of the rectal and genital cases, but to me on the sidelines it seems difficult to place very much credence in these findings with treatment extended over such long periods and an acknowledged spontaneous healing in 33 per cent of cases without any treatment. It seems that each injection produces headache and malaise in about three quarters of the cases but that usually only the first two cause a severe systemic reaction with chill, fever, joint pains, skin rash, etc., in a small proportion of instances the reaction is delayed for twenty-four hours and then is very severe and lasts several days.

In cases of marked rectal stricture colostomy is often necessary.

NONTUBERCULOUS URINARY TRACT INFECTIONS

(*Cystitis, Pyelitis, and Pyelonephritis*)

Therapy in these infections has been much altered by the introduction of the sulfonamides. Mandelic acid and methenamine (urotropin) still have occasional indications, but there is no longer any need to clutter up the pages of the book with descriptions of the other drug techniques.

Sulfonamides—These drugs have certain very definite advantages over mandelic acid which I shall list as a means of emphasizing the properties of the sulfonamides themselves. *First* They can be given in the acute stage of the infection which, especially in infancy, is a definite advance over the previous use of only diuresis and alkalization. *Second* Their action is not dependent upon the reaction of the urine. This not only frees us from the necessity of insuring an acid urine by means often objectionable to the patient but also enables us to overcome *Proteus ammoniae* and a few other less frequently encountered organisms which through their conversion of urea into ammonia prevent acidification of the urine, indeed Sickler (1940) has shown that the activity of the sulfonamides is actually somewhat greater in alkaline than in acid urine. *Third* When renal function is subnormal administration of mandelic acid is not only injurious but useless. Injurious because itself a renal irritant it also promotes acidosis by reason of the inability of the injured kidney to excrete it, and useless because the damaged kidney is unable to produce an acid urine in which the mandelic acid can exert its antiseptic action. These conditions do not apply to limit the activity of the sulfonamides for they appear in the urine in effective concentration even though the blood urea is well above normal. *Fourth* These drugs are apparently able very often to clear up infection in which there is an associated

chronic prostatitis due to the fact that they appear in the prostatic secretion in instances however, in which nonspecific prostatitis is found in the routine search for foci of infection, without urinary tract infection being symptomatically recognizable, these drugs have been of little or no value.

Sulfanilamide was early shown to be highly effective in the vast majority of cases but *Streptococcus faecalis* is completely resistant to it. Sulfapyridine has not been much studied as a urinary antiseptic. However, the studies of a number of workers, but principally Helmholz (1941), have shown that sulfathiazole is upon all counts the superior drug. (At the time I write the status of sulfadiazine in urinary tract infections has not yet been established though the report of Tinlaod *et al.*, 1941, indicates that it may be found to be as effective as sulfathiazole, in which case it will of course be preferred because of its lower toxicity. Sulfacetamide [albucid] too a drug not yet commercially available in the U.S. in early 1942, has been found highly effective. Welehr and Barnes [1941] have used this new agent satisfactorily in daily dosage of 20, 30 or 40 grains [1.3, 2 or 2.6 Gm.] With sulfathiazole all the following commonest invaders of the urinary tract are quickly overcome: *Pseudomonas aerogenes*, *Proteus ammoniae*, *Escherichia coli*, *Aerobacter aerogenes*, *Staphylococcus aureus*, *Streptococcus faecalis* other less usually encountered gram negative organisms are also successfully dealt with as well as the organisms of brucellosis and bacillary dysentery, each of which has in rare instances been reported as the causative agent in urinary tract infection unassociated with a primary attack of the specific disease.

Reasons for Failure—Enthusiasm for the use of the sulfonamides to the practical exclusion of all other drugs has run very high and it is difficult to find in the recent literature any satisfactory presentation of the subject of urinary tract infection as a whole, however, I believe I am justified in listing the following matters warranting consideration in connection with this new therapy: (a) Cases in which there is a drainage tube in place will clear symptomatically but the urine will not become sterile until drainage ceases. (b) Bladder tumors, other obstructions anywhere along the urinary channels and particularly stones, will greatly hinder sterilization. (c) Any considerable amount of stasis along the tract (stasis is the important etiologic factor in the infections of pregnancy) will prevent sterilization but it is said that the urine can be freed of bacteria even if there is a retention of as much as 3 ounces in the bladder, it requires less stagnation than this in the pelvis and ureters to interfere seriously with the action of the drugs. (d) Closed pockets of pus (abscesses, pyonephrosis, etc.) usually defy sterilization. (e) When there is a high degree of bilateral renal deficiency it may be impossible to produce a therapeutic level of sulfonamide in the urine without piling up a dangerous amount of the drug in the blood stream. (f) Crahtree (1941) says that in severe degrees of either acute or chronic infections of one kidney there is a tendency for the drug to escape so completely through the unaffected functioning kidney that an effective concentration in the affected kidney is not obtained.

Sulfathiazole Dosage—Dosage has been steadily decreasing. For example Cook (1940) said he thought the 60-grain (4 Gm.) daily dosage originally used could be well reduced to 45 grains (3 Gm.), and more recently (late 1941) he has been using no more than 30 grains (2 Gm.). Helmholz (1941) has stated that at least for *Escherichia coli* infections 12 to 15 grains (0.75

to 1.0 Gm) per day should suffice in average cases. Helmholtz also feels that 2 grains (0.13 Gm) five times daily should prevent the infections commonly associated with postoperative catheterization.

Sulfonamide Toxicity—See the separate chapter on this subject at the end of the book.

The following two drugs are retained because it is well to have more than one string to our bow.

Methenamine—Methenamine (urotropin) is excreted unchanged by the kidney and is not itself bactericidal but when it enters acid urine formaldehyde begins to be split off and gives the urine its bactericidal properties. Helmholtz has shown that the proper condition for its greatest activity is a urine of pH 5.5 or less. Since chlorophenol red paper or nitrazine paper (Squibb) indicates this degree of acidity, the practitioner's problem simply consists in maintaining a urine which will give a positive test with this paper while he is administering methenamine. The drugs principally used for this acidification have been sodium acid phosphate, ammonium acid phosphate, ammonium nitrate, and ammonium chloride. Ammonium acid phosphate has been shown to be the best acidifier and to cause the least gastro-intestinal irritation. Usual adult dosage is 30 grains (2 Gm) of the acidifying drug and 15 to 20 grains (1-1.3 Gm) methenamine four times daily. Helmholtz's (1937) method of using these drugs in children is a good model to follow for patients of any age. He begins with the acidifying salt alone $7\frac{1}{2}$ to 15 grains (0.5-1 Gm) four times daily and then when the urine reaches pH 5.5 starts giving methenamine 2 to 3 grains (0.15-0.2 Gm) four times daily for infants, 5 to $7\frac{1}{2}$ grains (0.3-0.5 Gm) for children of four to five years, and 12 to 15 grains (0.75-1 Gm) for children of six to fifteen years. Unless there is evidence of some injury by the drug which is unusual (frequency, hematuria, pain, skin rashes, excessive gastro-intestinal irritation) he continues the dual medication as long as is required to produce and maintain a negative urine, i.e. the urine is cultured at forty-eight hours and again each twenty-four hours and each time that it is found positive in the presence of pH 5.5 he increases the dose of methenamine 4 grains (0.25 Gm) per dose. In any case, even though the culture is negative very early, the drug is administered for five or six days. Helmholtz feels that to attempt treatment without control by culture is pure guesswork, since the urine may be rendered sterile in twenty-four hours or it may not become sterile in two weeks; however, it hardly seems likely that practitioners working under average conditions will be able to achieve quite this high ideal of basic methenamine administration on the result of repeated twenty-four-hour cultures of the urine. It is generally agreed that the drug is more often effective in bacillary than in coccocal infections, though some strains of *Escherichia coli* are extremely resistant.

Mandelic Acid—In mandelic acid, Rosenheim (1935) found an organic acid which, escaping oxidation in the body, was excreted intact to give bactericidal properties to the urine. The drug seems to be most effectively used in the form of calcium mandelate, which is tasteless and does not cause much gastro-intestinal disturbance; it will often also give a sufficiently acid urine so that acidifying salts (see Methenamine above) need not be used with it. The adult dose is 45 grains (3 Gm) at six-hour intervals, 4 doses—a total of 180 grains (12 Gm)—in the twenty-four hours. Helmholtz's method of administration may serve as model procedure, as in the case of methenamine.

(nbove) for children up to three years, $7\frac{1}{2}$ to 15, or even as much as 20 grains (0.5-1 or 1.8 Gm.), four times daily, from four to eight years 25 grains (1.5 Gm.) four times daily, children more than ten years may be started on 40 grains and can tolerate up to the full adult dose. The drug is said to be well flavored by prescribing it in solution in compound syrup of sarsaparilla, and also that if this is diluted with charged water at the time of taking root beer is very well imitated. The conditions are the same as in the case of methenamine so far as duration of therapy, culturing of urine, and acidity are concerned. For a comparison of this drug and the sulfonamides, see *Sulfonamides* above.

Local Application of Urinary Antiseptics—The sulfonamides are sometimes introduced into the renal pelvis directly through the ureteral catheter, this is apparently an effective type of therapy in selected cases. Austen (1940) has shown that absorption of appreciable amounts into the blood stream can take place when the drug is administered by this route. The sulfonamides are also used in 0.8 per cent solution for continuous irrigation or several times daily lavage of the bladder. The older solutions used for bladder irrigation are the following: silver nitrate, 1:10,000-1:5,000, potassium permanganate, 1:8,000-1:5,000, mercurochrome, 1:200, mercuriphen 1:10,000, gentian violet, 1:500, acriflavine, 1:8,000-1:6,000.

STONE IN THE URINARY TRACT

Kidney stones, or calculi, consist of amorphous collections of granules of urinary salts gummed together and embedded in a structureless albuminous substance. When their presence is made known, they may be large or small and may be embedded or lying free in the calices or pelvis of the kidney, or they may present as a foreign body obstructing the ureter. At times there is but a fluctuating aching pain in the loin of the affected side, or radiating into the lower back, the abdomen or leg. Constant or intermittent hematuria is oftentimes remarked, and sometimes there is the passage of "sand." Bladder symptoms, such as frequency, urgency and burning, are not unusual even when the bladder is free from lesions. The most characteristic manifestation of the presence of stone, however, is an attack of renal colic. The pain strikes quickly in the kidney region, but soon radiates down into the abdomen, the thigh and leg, the scrotum (or vulva), and sometimes into the opposite kidney region (the so-called "renorenal reflex"). There is nausea, vomiting and gaseous distention during such an attack, which may last for a few minutes to several days but probably endures for four to twelve hours in most instances. If complete obstruction occurs there will be hydronephrosis on the affected side and perhaps anuria, even though the opposite side is not obstructed (the so-called "reflex anuria"). Thus, the symptoms of renal lithiasis are the symptoms of obstruction, but why the stones form in the first place is one of the most venerable of medical mysteries. The disease is unilateral in most cases, but at the present time there is no way of foretelling the tendency in a patient to develop stones on the other side. Stones in the bladder may

be either kidney stones halted there by obstruction, or they may originate there as deposits on some introduced foreign substance or as encrustations on inflammatory lesions. In general the symptoms of stone in the bladder are not very characteristic. The most usual complaints are of frequency, hematuria, the passage of sand, difficult urination, sudden stoppage in the flow of urine, and pain running down to the head of the penis. Tuberculosis, prostatic enlargement, and vesical neoplasm must be carefully ruled out.

The earliest known urinary calculus was found among the pelvic bones of a boy about sixteen years of age in an Egyptian grave of a period some time prior to 4800 B.C. The treatment of vesical stone was made a specialty early in the Middle Ages by quacks who "cut" only for stone, most of the operations being performed on children, and these operative procedures were not effectively got out of their hands until the sixteenth century. In our present era, vesical calculus is predominantly a malady of elderly men, at least in the highly civilized countries, but it is said to occur still with great frequency in the young in hot dry climates. Urinary calculi occur much less frequently among Negroes than among whites, the incidence in all races is said to be very low in wet tropical countries. Apparently, Domenico Marchetti in 1633, performed the first operation for renal calculus.

THERAPY

In this edition of the book I shall not review all the diverse views regarding the etiology of stone because to do so would require a great deal of space and perhaps in the end really not greatly enlighten the reader. However, the possibility that Randall (1940) is correct should be mentioned. He says that no matter what dyscrasias, deficiencies, or what not dictate the deposition of particular salts, there is in every case of primary renal calculus a typical microscopic pathologic process in the wall of the renal papilla which precedes the gross appearance of stone—and he has convinced himself at least that this is true.

Fluids—The opinion is unanimously held that the forcing of fluids is indicated for all kinds of stone since the more dilute the urine the less chance there is for precipitation of salts to occur. Contrary to prevalent opinion a dilute urine does not preclude an acid urine.

Infection and Stasis in the Urinary Tract—Both these conditions are known to contribute to calculus formation. Sulfathiazole is proving a boon in clearing up such infections, fortunately it is effective against the common urea splitting organisms which enhance precipitation of phosphates and carbonates by increasing the alkalinity of the urine. Stasis is a matter often requiring the most expert urologic handling.

Hyperparathyroidism—A few years ago, Albright and his associates at the Massachusetts General Hospital showed that tumors of the parathyroid glands giving rise to high blood calcium, with or without other signs or symptoms of hyperparathyroidism, are sometimes associated with recurrent stone, and that surgical removal of such tumors may correct the lithiasis. However, Griffen *et al.* (1938) found hyperparathyroidism to be an etiologic factor in less than 0.2 per cent of 1206 cases of renal calculus at the Mayo Clinic.

Vitamin A Therapy.—The Council on Pharmacy and Chemistry, in 1942 still does not accept the contention of Higgins, of the Cleveland Clinic, that

high vitamin A feeding is of considerable value in dissolving and preventing the recurrence of stones. Higgins employs in addition to vitamin A (see Xerophthalmia for methods) an acid ash diet. Oppenheimer and Pollack (1937) studied this matter very thoroughly in 27 patients at the Mount Sinai Hospital in New York and failed to confirm Higgins' findings: in none of the patients did the calculi show even partial solution though the patients were on the diet for from six to sixteen months, in 5 the size of the calculi increased and in 1 a new stone formed. Erickson and Feldman (1937) failed with the Higgins regimen in their 11 patients who remained faithful to the treatment for six to nine months. In the patients of Erickson and Feldman, and also in those of Long and Pyrah (1930), the vitamin A therapy did not raise the systemic vitamin A reserve as it normally does in patients not afflicted with stone. This is interesting, as are also the facts that (a) in Syria, according to Brown and Brown (1941), the vitamin A intake is low and the incidence of vesical stone in children is high, (b) the South African native Negro (Bantu) does not form stone, according to Vermooten (1937), and his diet is rich in vitamin A, has an acid ash and is extremely low in calcium. Perhaps there is something of value in this vitamin A deficiency theory, but it simply is not proved as yet.

Recumbency.—It is now agreed that an active individual who has been using calcium constantly in renewing bone structure is in danger of developing stone when he becomes inactive or is incapacitated by a bout of illness or through immobilization in a cast, enlurem and phosphorus are released from bone under these conditions and their concentration in the urine greatly increased. In addition there is likely to be stasis somewhere along the urinary tract at least at intervals in such individuals, which invites both infection and stone formation. The prophylactic measures to be taken in such cases consist in pushing fluids and changing posture as frequently as is possible consistently with orthopedic or other considerations. Boyd (1941) likes to place patients for at least an hour or two daily on the ventral surface of the body and to have them drink a large amount of water before shifting into this position. Active movement and massage of all limbs not splinted is to be practiced daily.

Calcium Phosphate Stones.—In addition to pushing fluids the usual procedure is to use in these patients a diet with an acid ash (see below) in order to keep the salts in solution, theoretically the dissolution of the stone itself might occur in this acid urine. However, it is also to be remembered that an acid ash diet will also cause loss of calcium and phosphorus from the bones and thus increase the concentration of these elements in the urine. Flocks (1941) warns that in some instances, *i.e.*, if the urinary calcium is high (daily normal, 200 mg.) in the beginning, one should use the acid ash diet with great caution for fear the bad might outweigh the good effects. Albright (1937) points out that if one does not succeed in obtaining an acid urine (a pH of 5.5 is usually sought) then certainly the results will be bad, for the acid ash diet will liberate salts from the bones which will be precipitated in the alkaline urine (infection with urea splitting organisms is of course the greatest factor working against achievement of an acid urine). A measure often taken is to use acidifying drugs (see Urinary Tract Infection) in addition to the diet, but upon the whole this has not been helpful because the increased acidity of the urine has been paced by the increased liberation of

calcium and phosphorus from the bones. Latterly, Albright (1939) and his associates at the Stoea Clinic of the Massachusetts General Hospital have been experimenting with acids to be introduced from below by a catheter solutions of sodium citrate-citric acid at a pH of 4.0 and of hexametaphosphate have been reported as giving good results, but I believe that findings of general clinical applicability have not been made as yet.

It has been stated upon occasion that the Sippy regimen as used in peptic ulcer, and the self prescribed alkali dosing of many dyspeptics tend to promote the formation of calcium phosphate stones, but exact studies of this point have yielded findings strangely at variance. In Eiscle's (1940) 505 patients with stone there was a history of treated peptic ulcer in 8.5 per cent, in Kretschmer and Brown's (1939) series of 1260 patients there was a similar history in only 1.2 per cent.

Uric Acid Stones—The treatment consists in using an alkaline ash diet (see below) because the urates thus formed are more soluble than uric acid itself. Many of these patients have gout, a few have not, in all the usual practice is to employ the low-purine diet (see below).

Calcium Oxalate Stones—Since calcium oxalate is soluble both in acids and alkalis, nothing is to be expected from an attempt to change the reaction of the urine. Fluids are to be pushed. It is the practice in some quarters to prescribe a diet low in oxalates (see below), but I do not know how many men are willing to guarantee nonrecurrence of the stone as a result of using it.

Cystine Stones—The patient with cystine stones is the victim of an hereditary disturbance in cystine metabolism. Cystine precipitates in an acid urine, so the treatment consists in using an alkaline ash diet (see below).

Diets—The several diets referred to above are the following. *Acid-ash* meats, fish, eggs, cereals, little fruit and vegetables, no milk or cheese. Albright (1941) seems to feel nowadays that the adult, particularly if he is sedentary, should not drink milk or eat cheese even though he has not yet shown any stone tendency. *Alkali ash* fruits, vegetables and milk, as little meat, fish, eggs and cereals as possible. *Low-purine* (see Gout). *Low-oxalate* no potatoes, beans, spinach, tomatoes, beets, endive, rhubarb, asparagus, strawberries, raspberries, pears, plums, figs, currants, cocoa, chocolate, tea, and sweets in general. MacDonald (1936) favors the use of hard cider for its malic acid content.

Spa Treatment—The drinking of large quantities of water, frequently referred to above, has been asserted to be of value since ancient times. Certain mineral springs, of which every continent has its favorites, are said to have the power to fracture stones, with the fragments being ultimately passed, at the least, much water is drunk at the spas and the music is often most enjoyable.

Surgery—There is nothing to say in a book of this sort of course except to lament under this head the fact that a woefully large proportion of the victims of stone must still submit ultimately to instrumental or operative interference. Recurrence, however, is as much a hugaboo to the surgeon as to the urologist.

Renal Colic—In the presence of severe pain, morphine sulfate, $\frac{1}{4}$ grain (0.015 Gm), or dilaudid, $\frac{1}{32}$ grain (0.002 Gm), combined with atropine sulfate, $\frac{1}{100}$ grain (0.0006 Gm), is given hypodermically, often the opiate has to be repeated and frequently will not relieve this pain at all. Colston

(1936) reminds us that on the basis of opium's ability to stimulate ureteral musculature it would be much better to use atropine in combination with a sedative. Bauer *et al* (1931) injected 20 cc of 5 per cent calcium chloride solution intravenously in a small series of cases, in nearly all instances relief was prompt and great enough to permit the patient to go to sleep without an opiate, in 1 case calcium chloride injection succeeded where morphine had failed. Heat, best applied by placing the patient in hot water in the bath tub, is often effective in relieving this pain, but some individuals are in such agony that they cannot remain in the tub. Sometimes resort to general anesthesia is necessary. O'Connor (1939) has given subcutaneous injections of 1 cc of 1:2000 solution (0.5 mg of the active substance) of prostigmin methylsulfate at three to four hour intervals for four doses in 52 patients in whom surgical procedures were not critically indicated and cystoscopic manipulative measures had not been successful, he felt that passage of the stone was hastened in a good many instances but of course there was no way in which to make sure of this. Prostigmin's action would be just the opposite of that of atropine, *i e*, instead of relaxing the ureter it would stimulate its propulsive action. I should think one would have had to make certain in each case that the ureter was of normal conformation and completely unobstructed below the stone before beginning the use of this drug.

DISEASES OF THE NERVOUS SYSTEM

DISEASES OF THE NERVOUS SYSTEM

SYDENHAM'S CHOREA

(*St Vitus' Dance*)

Chorea is one of the common diseases of childhood. It may occur at any age but most cases are seen between the fifth and fifteenth years. The disease is more frequent in occurrence in girls than boys and in the poorer than in the richer classes. Negroes and full blooded American Indians are rarely affected. When the child is brought to the physician for the first time, the parent usually states that for a week or more it has been fidgety, emotional and excessively clumsy. Upon observation the patient will be seen to be in almost constant jerky motion, grimacing and purposeless movements of the face and head are the most usual phenomena, but any part of the body may share in the wriggling or writhing motion. There is also much muscular incoordination, as shown frequently by the overpassing of objects with the hand or in difficulties in locomotion. Except in the most severe cases, these movements cease during sleep and are to some extent under voluntary control, at least firm, kindly commands will often cause them to be restrained for a brief space. The speech is often choppy in character, sometimes being entirely unintelligible, in a relatively few cases the child is entirely unable to speak. The usual mental involvement is in the direction of dulness, carelessness and loss of memory, though not infrequently this state is broken into by intense emotional storms. Appetite and the general condition usually remain good despite some loss of weight and the development of more or less anemia. Headache and muscular weakness are always complained of. The most frequent complication is endocarditis. The duration varies from several weeks to many months, sometimes to more than a year. Death is very rare, and when it occurs is due to general wasting plus intercurrent sepsis and heart failure. Relapses and recurrences are not uncommon in this disease.

Since the middle of the last century the effort has been made, both in Europe and America, to link together rheumatic fever and chorea. Undoubtedly the presumptive evidence in favor of such an association has great weight but the contention is not yet proved. This much seems to be established, however (Parrish *et al.*, 1937, Sutton and Dodge 1938, Usher, 1938) the child with chorea will develop the rheumatic type of heart disease in from 20 to 50 per cent of instances even though he does not develop the typical joint and other symptoms of acute rheumatic fever. Chorea has also many times been seen to follow an attack of one of the other infectious diseases, particularly scarlet fever, a disease also thought to be of streptococcal origin.

Sydenham provided the classical description in 1686. During the early part of the fifteenth century, one of the waves of crazy fanaticism which characterized the period took the form of a dancing mania among certain groups of physically degenerated people, one such group, "dancing" toward

the chapel of St. Vitus in Zabern gave the disease its other title—though the etiology of this affair of perverted crowd psychology bears probably no relation to that of the disease we have here under consideration.

THERAPY

Rest—Absolute bed rest is the most important single element in the treatment of chorea not only because it seems to promote subsidence of symptoms but also because of the possibly associated rheumatic fever and the ever lurking endocarditis. Howell (1935) stresses the importance of keeping children and other visitors away and of keeping the room darkened. Whether this rest should be secured within or without the family circle must be decided in each individual case. The sedative drugs (for a list see *Insomnia*) are by no means contraindicated and can perhaps be used with profit in most severe cases, of course their dosage must be reduced according to the child's size and age. Poynton adds chloralhydrate to the list of useful sedatives in this disease, 5 grains (0.32 Gm.) three times daily. In some cases Howell gives 5 to 10 grains (0.3–0.6 Gm.) urethane. At times general anesthetics must be employed. Sint and McDade (1933) have given 1 to 2-cc intravenous injections of evipan sodium, Cole (1936), avertin rectally, 0.1 Gm. per kilogram body weight. Duckett Jones (1935) strongly advises the trial of stramonium, powdered (not as tincture), before resorting to these more heroic measures in violent cases. Tepid sponge baths are nearly always soothing and in some instances an excellent reaction follows upon the use of the ice pack in uncomplicated cases (i.e., wrap the patient in blankets with a sheet wrung out of very cold water next to his skin).

Salicylates—Those who look upon chorea as a rheumatic meningoencephalitis consider the salicylates to be indicated. For a description of their employment see *Rheumatic Fever*. Mutch (1934) prefers calcium aspirin for its alleged triple action: antirheumatic, sedative, corrective of calcium deficiency. As a matter of fact, I know of no studies that prove the salicylates to be of direct value in chorea.

Arsenic—This drug has been employed empirically for many years. Usually it is given in the form of Fowler's solution (the solution of potassium arsenite of the U.S.P.) in ascending doses. The method most often employed is to begin with 3 minims (0.2 cc.) three times daily and increase this dose by 1 minim (0.06 cc.) each day or every other day, until 10 minims (0.6 cc.) are taken at each dose; this dose is then continued for a week unless toxic symptoms appear earlier. The symptoms most often presenting are puffiness under the eyes or about the ankles or gastro-intestinal disturbances. The possibility of arsenical neuritis should always be borne in mind, however, for this rather serious consequence of prolonged arsenical therapy has been seen without any preliminary edematous or gastro-intestinal symptoms more often than is commonly believed. I know of no statistical studies of the efficacy of arsenic treatment, the presumptive clinical evidence is far from being unanimous in its favor. Of course the disease is almost too variable in severity and course to make careful studies of nonspecific remedies possible, however, Abt's statement made in 1916 would probably find more endorsers today even than it did at that time. 'I want to say a word about arsenical treatment and rest in bed. For years I have had children brought to me with chorea. One of my colleagues might have a case in an opposite

hed I would say, 'You treat with arsenic and I will treat without' The baby without arsenic, but with rest in bed, would recover just as rapidly as the other child treated with arsenic. The child's term in the hospital would be no longer than with the arsenical treatment. It seems to me the treatment of these cases of chorea, especially in neuropathic children without heart lesions and no evidence of infection, is to take them away from their family, feed them, keep them absolutely quiet in bed, give them hot baths, and they generally recover in a short time.

Nirvanol.—It is claimed that this drug is often effective in sharply checking chorea, but it is a very toxic agent and the great majority of observers no longer feel that its use is justified.

Fever Therapy.—Since 1931, Sutton and her associates have been treating cases by induction of hyperpyrexia. In the beginning they used typhoid paratyphoid vaccine intravenously, beginning with 0.05 or 0.1 cc. and determining the subsequent daily dosage by the reaction, the aim being to attain a temperature of 104° to 106° F. (40° to 41° C.). If necessary they administered a second dose on the same day and continued treatment, with occasional days of rest, until all signs of chorea disappeared. Latterly it has been recognized that the physical means of producing fever are equally effective and cause the patient less discomfort, there are now a great many observers who testify to the value of the hyperthermia in this disease. Most cases are said to respond favorably and quickly, but the technique does not yet seem to be uniform. Some men give treatments at 104° to 106° F. (40° to 41° C.) for two hours daily, others at only three- or four-day intervals, in Bennett and Hoekstra's (1941) 17 cases, an average of eight daily treatments was necessary to effect cure. The consensus is that cardiac involvement does not contraindicate fever therapy.

HICCUP

Hiccup is produced by a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It occurs not infrequently in the fetus, detectable as regular, short, quick jerks at the rate of 15 to 30 a minute, they are visible and palpable, and the muscle sound of the diaphragm as well as of the body striking the uterine wall can be heard. If occurring during labor it is sometimes not interrupted by the birth of the child and continues for a short time afterward, DeLee has seen a baby born hiccuping so loudly that it could be heard in the next room. The greatest incidence of hiccup in infancy occurs during the first three months, principally among breast-fed babies, probably due to overdistention of the stomach with food and swallowed air. In adults it may be caused by inflammatory or pressure irritation of the phrenic nerve or reflexly through the vagus. It may be a symptom of almost any disease but the entities with which it is most often associated are nervous epilepsy, encephalitis, brain tumor, Addison's disease and functional organic traumatic and acute infectious processes anywhere in the gastrointestinal tract. Apparently it also occurs reflexly in diseases

of the pleura and pericardium as well as in some of the chronic constitutional diseases. And some surgeons of experience, as pointed out by Wade (1932), look upon the occurrence of postoperative hiccup as a warning of impaired renal function. Byrnes (1935) describes some cases apparently occurring as an unusual form of tabetic crisis. In addition to which there are the idiopathic and epidemic cases—the latter believed by MacNalty (1937) to be manifestations of epidemic encephalitis of a mild type.

THERAPY

Most cases in infants are transitory and of no serious importance. The infant should be not permitted to suck the breast when it is empty or the bottle in such way as to take in large quantities of air, and after feeding it should be held upright to aid regurgitation. Sometimes it is necessary to give a spoonful or so of hot water or weak sodium bicarbonate solution or diluted lemon juice. Of course the more serious cases may also be seen in infants. In adults the most important thing, of course, is to make every effort to locate and treat the underlying cause of the trouble, which is very much easier to say than to do. The actual measures directed against the spasms are of course legion, as is the case in all maladies of vague and variable etiology, the following seem most often to have been of assistance.

Sedatives and Anesthetics—The whole gamut is run—bromides, chloral, barbiturates, paraldehyde, belladonna, compound spirits of ether (Hoffmann's anodyne), hyoscine, opiates, apomorphine, and the general anesthetics. Cadham (1925) says that benzyl benzoate found greatest favor with physicians during the well known Winnipeg epidemics, but he felt that evaluation of any remedy was very difficult. It may be suspended with mucilage of acacia or prescribed in one of the higher alcoholic vehicles, such as the compound tinctures of cardamom, gentian or cinchona (all of which have some carminative value), or the tinctures of sweet or bitter orange peel. Ruhrah preferred to give the drug in sweetened milk. See also the sedative measures employed in whooping cough, these are sometimes successful here also. Deep anesthesia is sometimes successful, but it was induced with both ether and chloroform in Campbell's (1940) case without effect either time.

Benzedrine Sulfate—Shaine (1938) has reported good results following hypodermic injection of $\frac{1}{2}$ to $\frac{3}{4}$ grain (10 to 20 mg.) of this drug.

Cocainization—In persistent cases, Lichtenstein (1928) obtained good results with a dilute cocaine-epinephrine solution containing a very small amount of phenol, applied to both nostrils on pledgets of cotton.

Carbon Dioxide—Carbon dioxide in various proportions with oxygen delivered from the usual apparatus, has been very favorably reported upon a number of times. Golden (1931) describes a simple, inexpensive method of inducing the inhalation of carbon dioxide, which has been effectively used by him. An ordinary paper bag of medium size and strength is placed over the patient's face and so held that it tightly encloses the mouth and nose, thus inducing rebreathing of an atmosphere whose carbon dioxide content steadily rises. Five of his 6 patients were relieved in from three to six minutes, one of them had been hiccuping for two days.

Fluids—In postoperative cases in which impaired renal function is suspected the "pushing" of fluids not infrequently brings relief.

Lavage—Continuous siphonage of the stomach through the Levine tube has been successfully employed a number of times

Phrenic Nerve Operations—Weeks (1931) believes that in intractable cases, when everything else has failed, the patient should be examined fluoroscopically to determine which side of the diaphragm is involved, the phrenic nerve on that side should then be exposed under local anesthesia, a stout silk ligature passed about it, and the nerve anesthetized—which seems to bring relief of about eight hours. Following this, traction is to be tried, this failing the nerve can be crushed, failure of both points toward anastomosis below the site of section or blocking, and indicates avulsion. In cases of bilateral involvement, it is said that the operative procedures can be bilaterally performed. Campbell (1940) has recently reported a case in which bilateral phrenicotomy was required for cure.

Household Remedies—The remedies tried with varying degrees of success in mild attacks are pressure or application of an ice-cap on the back of the neck, holding the breath, swallowing a bolus of food, tickling the nose to induce sneezing, gentle compression of the upper part of the thyroid cartilage, sipping cold drinks, swallowing finely cracked ice, prolonged traction of the tongue, painting the uvula with an irritant such as tincture of iodine, inhaling fumes of ether or smelling salts, drinking some gastric irritant such as Worcestershire sauce or an ounce or so of whisky neat, pressure on the upper lip or eyeballs or ribs, holding the breath, sudden fright.

TRIGEMINAL AND ASSOCIATED TYPES OF NEURALGIA

Trigeminal neuralgia is a disease of the gasserian ganglion, affecting one or all of the branches of the trigeminal nerve, the infra orbital division is the most frequently affected, then the mandibular, and then the ophthalmic. The pain comes "out of a clear sky," and is described as shooting, stabbing, lightning like, cutting, etc. It lasts but a few seconds to a few minutes, but during the time of its presence is perhaps as severe as any that man is ever called upon to experience. The patient remains motionless with a fixed grimace and oftentimes with some defensive posture of the body as a whole. Relief is usually complete upon termination of the spasm. Such an attack may be precipitated by any minor essential movement, such as opening the mouth, swallowing, winking, talking, washing the face, brushing the teeth, etc. In the beginning there is often a considerable interval between seizures, and there may even be an asymptomatic period of several months to years, but finally in practically all cases the pain becomes continuous and affects all three divisions of the nerve. It is my belief that spontaneous recovery has never been recorded. In untreated cases, death may result from inanition consequent upon inability to eat or sleep. Rarely, very careful general and neurologic examination will be required to rule out peripheral lesions as the cause of this type of pain—lesions involving the nerve trunks, posterior roots or root ganglia, lesions of the brain stem or in the optic thalamus lesions in higher associated brain centers. Typical of the

sort of pseudotrigeminal neuralgia which may be encountered is the case of Banyai (1936) in which pain was completely relieved by phrenic nerve block and was thought to have been referred to the trigeminal nerve from the site of a tuberculous diaphragmatic pleurisy

Tic douloureux involving the glossopharyngeal nerve is manifested as pain extending from the tonsillar region into the ear, relief of pain upon cocainization of the nasopharynx establishes the diagnosis. Tic involving the occipital nerves arising from the first, second and third cervical nerves is differentiated through relief achieved upon procaine infiltration beneath the scalp. Other, very rare, types are those known as Sluder's, Jacobson's and Hunt's neuralgias

Trigeminal neuralgia by far the most frequently encountered of these maladies is a disease of those in or past the middle years of life, and is of unknown etiology, though its association with carious teeth has been often remarked, Harris (1930) feels that an hereditary tendency is not rare. It was first described by Avicenna (Ibn Sina), he who was called 'the Prince of Physicians' at the court of more than one caliph at Bagdad about the year 1000 of our present era, the first accurate description satisfying the present day criteria was that of Fothergill, in 1773

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The Older Analgesics—None of the sedatives or analgesics are consistently of value in trigeminal neuralgia save only opium, and even it must be given in rapidly increasing doses in order to control the pain, it is therefore used only when trichlorethylene fails and surgical relief cannot be obtained or is refused. It is also stated in the older literature that doses of U.S.P. tincture of aconite sufficient to cause considerable lethargy and a slowing of the pulse to 50 or less, *i.e.*, beginning with 15 minims (1 cc) three times daily and increasing will sometimes afford temporary and partial relief.

Trichlorethylene—This is a strong, sweet smelling white liquid which was used for industrial purposes in Germany during World War I and was accidentally discovered to be of value in relieving trigeminal pain when Plessner presented before the Berlin Medical Society, in 1915, several workers suffering from chronic poisoning by the substance. The present method of administration is to place 20 to 25 drops on a piece of gauze and inhale (lying down because slight dizziness and drowsiness are occasionally caused) until there is no more odor, this three or four times daily for a period of four to six weeks. In those obtaining relief, it is the practice to continue the treatment by inhaling on three consecutive days every two or three months. Glaser (1931), in reporting 15 of his own cases summarized the results obtained in the 177 reported cases as follows: (a) complete relief about 15 per cent, (b) partial relief, from 13.3 to 74 per cent. Since then Horrax and Poppen (1935) have stated that of their 60 patients nearly one half obtained sufficient relief that they did not feel obliged to submit to more radical treatment for periods of six months up to six years, in the other patients injection or surgery had to be resorted to very quickly. An advantage of the drug, which would seem to make its trial worth while in any beginning case, is that it does not cause local numbness, as do injection or the surgical procedures. There are many cases of severe poisoning on record as a result of prolonged contact with the drug industrially, but these things need not

be feared when it is used therapeutically. However, Eichert's (1937) report indicates the advisability of close surveillance of the patients and frequent checking of the dosage, for he has had 2 patients who, as a result of grossly excessive dosage, developed temporary but very alarming mental symptoms.

Typhoid Vaccine—Schmidt and Sullivan (1939) have used typhoid vaccine intravenously at biweekly intervals, starting with a dose of 10,000,000 organisms and building up with increments of the same or double this size until mild fever responses are obtained. Of their 18 patients, 5 obtained complete relief, 5 over 80 per cent relief, 3 obtained 50 per cent or less and required alcohol injections. In 4 there was complete relief but this was only temporary and injection was required, 1 patient experienced no relief at all and resection was required.

Cobra Venom—Schmidt and Sullivan (1939) failed to effect relief with this agent in the 3 cases in which it was tried, Behrmann (1940) succeeded in 1 case and obtained partial success in another.

Alcohol Injection and Surgical Treatment—The surgical measures available at the present time for the relief of trigeminal neuralgia are (a) alcohol injection of the nerves near the foramina of exit from the skull, (b) alcohol injection of the gasserian ganglion, (c) the operation of peripheral avulsion of the sensory root, and (d) radical division of the sensory root. Nerve injection and avulsion would seem to afford relief for a period of from nine months to several years, radical division affords permanent relief (unfortunately painful paresthesias sometimes follow), relief from the ganglion injection seems to be permanent in most cases also. All of these measures have their advantages and disadvantages, their advocates and detractors. I believe the selection of the type of treatment to be employed in a given case is so serious a matter that it should not be treated of merely in passing in this book. However, I permit myself to counsel the reader to entrust his patient only to a surgeon who has had much cadaver and actual operative experience in these matters. Injection and surgical procedures are likewise available nowadays for the other rarer types of neuralgia mentioned above.

POSTHERPETIC NEURALGIA

(See *Herpes Zoster*)

SCIATIC NEURALGIA

The majority of the victims of sciatica are males between the ages of thirty and sixty years. In most cases the pain begins in the sciatic notch or in the lower lumbar region and gradually extends down the course of the sciatic nerve. In the beginning this pain is often merely a dull ache that bothers the patient very little, but it finally becomes burning, sticking or

lancinating in character, and radiates downward from the sciatic notch along the posterior aspect of the thigh into the calf muscles and foot. In many chronic cases the pain is ultimately confined to the outer aspect of the calf and foot, where it becomes persistent and causes as much discomfort as the pain in the thigh and buttock during the early stages. Tender spots and areas of paresthesia are frequently noted. Some individuals find the prone position on the unaffected side, with thigh and leg slightly flexed, absolutely essential for partial comfort, while others, particularly in the later stages, find walking gives greater relief. An attack of sciatic neuralgia may be relatively mild and persist for only a few days, but severe cases are protracted for weeks to months, during which time the patient is entirely incapacitated and suffers severely. Recurrence is the rule.

Pain due to sacro iliac strain, arthritis of the lumbar spine and of the lumbosacral and sacro iliac or hip joint, anatomic anomalies, intervertebral disk lesions, and pelvic and cord tumors must be ruled out in every case of suspected sciatic neuralgia.

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Removal of Foci of Infection—Whatever may be the true cause of sciatica, i. e., whether it be a ganglionitis, a periganglionitis, a neuritis, or an "idiopathic" neuralgia, it is claimed that the removal of all ascertainable foci of chronic infection brings about a more satisfactory result in this disease than in any other. The immediate response is often an increase in the severity of the symptoms, but the end result is said to be many times most gratifying. Therefore some men feel it of paramount importance to eliminate all possible foci of infection whenever sciatica is diagnosed—certainly a huge mound of teeth has piled up outside the jaws of American citizens in recent decades, I wonder how much sciatica has been cured.

Rest, Analgesia and Physical Therapy—In the early stage of an attack, complete rest in bed and the application of some form of heat along the course of the nerve, especially in the gluteal region, are efficacious measures. If combined with the salicylates as used in the treatment of acute rheumatic fever, the case is often controlled, though it is doubtful if these procedures lessen the total duration of the attack. Codeine sulfate, 1 gram (0.06 Gm.) or even full doses of morphine or dilaudid, must sometimes be used in the beginning of very severe cases. Counterirritants are not beneficial and massage only aggravates the symptoms. Oftentimes it is helpful to place boards over the springs of the bed and to use a mattress of the pad and not the spring type above them. Buck's extension, with 8 to 10 pounds may be useful in some cases though the pain is often exaggerated in the beginning. A corset or belt, especially devised for individual cases is many times helpful in ambulatory patients.

Injection Treatment—Many severe attacks of sciatica, attacks that would normally last for many weeks or months if treated only by the above described measures have been reduced in duration to only a few days by injection of physiologic sodium chloride solution. Complete and permanent relief was obtained by Craig and Ghormley (1933), Mayo Clinic in 52 per cent of 80 patients. I give the technic of *epidural injection* as described by Strauss.

The epidural space in an adult begins at the lower edge of the first

sacral vertebra, where the dura ends. It extends down to the sacrococcygeal articulation. At this level the injections are made. There are certain landmarks by which this opening, the foramen sacrale superius, may be identified. It lies at the end of the crest made by the spines of the sacrum. It has the shape of an inverted V or U, and is about 1 cm wide and from 1.5 to 2 cm in length. It is bordered laterally by two prominences, the cristae sacrales laterales, which are usually easily felt by the finger. The opening is covered by a dense fibrous ligament, the ligamentum sacrococcygeum. The opening lies generally 2 cm above the end of the gluteal fold.

'The needle used for the injection should be about 8 cm in length, and 1 mm in caliber. I have used an ordinary steel needle previously tested as to its flexibility. If greater flexibility is desired a needle made of platinum-iridium may be used, but a broken needle need cause no alarm; it will do no harm if allowed to remain in the epidural space. The needle is to be inserted to a depth of 6 cm to reach the second sacral vertebra. There is no danger of entering the subarachnoid space, because the dura ends at about the level of the first sacral vertebra; however, to be certain that this space has not been entered, it is well to wait for a few minutes before injecting to see whether there is an escape of cerebrospinal fluid. If possible when inserting the needle, one should place the patient in the knee-chest position in order more easily to locate the landmarks. If the injection is made with the patient lying on the side with the knees and thighs flexed the landmarks are not so easily discerned, and the gluteal fold usually lies above the foramen. It may be difficult, if not impossible, to enter the epidural space of very stout persons, especially of stout women. In such cases recourse must be had to the nerve injection.

'It has been my custom to anesthetize the skin and tissue overlying the foramen and the ligament with novocain. In doing this one must be careful not to cause much swelling which might obliterate the landmarks. After the needle has been pushed through the skin, considerable resistance is met at the ligament. Once this resistance is overcome, the needle glides into the epidural space. If the patient is in the knee-chest posture, the needle is inserted into the body at an angle of 45 degrees. After it has passed through the ligament the needle is held so that it is horizontal to the body. During the injection, the patient lies on the affected side.

'The injection consists of warm sterile physiologic sodium chloride solution. To the first 10 or 20 cc of solution is added 0.125 Gm of novocain with epinephrine, and a few minutes are allowed to elapse after their injection to obtain the full benefit of their anesthetic effect. In all from 60 to 80 cc of solution are injected at a time.

'The injections are given at forty-eight hour intervals. They may be given in the office, and the patient will have no difficulty in going home. It is preferable, however, for the patient to remain in bed during the intervals. The average number of injections required is three. Occasionally it may be necessary to give five, but sometimes two or even one suffice to relieve the condition. The most difficult cases to cure are the chronic ones in which the pain is along the outer aspect of the thigh. There have been no untoward results from the epidural injections. The knee jerk on the affected side has disappeared for a short time, and sometimes the patient complains of delayed micturition, but these symptoms soon disappear.'

The technic of the simpler injection of the nerve in the buttock is described by Burt (1930) as follows "The patient lies on his face and a pillow is placed under the pelvis to raise it slightly. The position of the sciatic nerve is marked with a dab of iodine, this position is most easily obtained by placing the thumb on the ischial tuberosity and the middle finger on the tip of the great trochanter. The tip of the index finger will fall naturally on the nerve as it emerges from the lower border of the piriformis muscle. The exact position is confirmed by detecting the maximum point of tenderness. It is advisable to use a lumbar puncture needle, 10 cm. in length—on entering the nerve sheath the patient will feel a pain shooting down to the foot. Inject 20 cc. of the solution (10 cc. of 1 per cent novocain made up to 100 cc. with physiologic saline solution) very slowly and leaving the needle in position, refill the syringe. Having fixed the syringe in position slightly withdraw the needle and push upwards into the piriformis muscle and inject a further 50 cc. Even if the saline does not penetrate the sheath of the nerve relief may be obtained."

Fever Therapy—Of course with the present vogue of fever therapy, sciatica has also come in for its share of attention, I have seen no report of a series of cases in which it was possible to determine how much of the claimed relief was definitely attributable to the hyperpyrexial bouts. Fever therapy methods are under Syphilis.

Surgery—Several orthopedic operations have been devised for the relief of sciatica and it seems that in selected cases each of them has some successes to its credit. Recently Freiberg (1937) has reminded us that the piriformis muscle is the only one which bridges the sacro iliac joint and that in doing so it is in extremely close relationship to the sciatic nerve. Spasm of the piriformis as a result of sacro iliac disease might conceivably involve the nerve, at any rate, Freiberg has put the matter to the test and in 2 cases obtained relief by simple operations on the muscle. This anatomic approach to the matter is an attractive one, but I do not know to what extent orthopedists have felt justified in adopting Freiberg's suggestions.

MÉNÈRE'S DISEASE

This is a malady characterized by recurring attacks of deafness, tinnitus, nausea and vomiting, and dizziness in which objects rotate or jump rapidly. It is hebeved that Martin Luther was suffering one of these attacks when he hurled the famous ink pot at the Devil who was plaguing his ear. Ménère's description established the clinical entity in 1861. Atkinson's (1941) hypothesis that the syndrome results from vasomotor disturbances which are in some instances allergic in nature, is interesting. Furstenberg *et al* (1934) have latterly been reinvestigating the proposition made some years ago by Danish observers that a waterlogged labyrinth associated with disturbances in salt and water metabolism underlies the syndrome. Talbott and Brown (1940) feel that a partial depletion of tissue potassium may lie at the root of the trouble. Dandy (1941) seems still to feel that the trouble lies in the

eighth nerve itself rather than in the end organs. Practically all of the victims are in or past middle life, the left side is more often affected than the right. The onset of the attack is usually very sudden and violent, the patient may be incapacitated for a few seconds, a few hours, or a few days, between attacks he is usually completely free from symptoms.

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Low Sodium-High Potassium—Furstenberg *et al* (1934) reported good results with a diet of low sodium content coupled with the intermittent ingestion of ammonium chloride. This treatment not giving great satisfaction in the hands of all workers, Talbott and Brown (1940) have proposed the use of a diet of normal sodium content but proportionately higher in potassium. This regimen is very simple since it merely comprises the taking of a normal diet plus 6 to 10 Gm ($1\frac{1}{2}$ to $2\frac{1}{2}$ drachms) of potassium chloride in aqueous solution daily. (The matter of low sodium high potassium regimens is discussed fully in Chronic Nephritis.) All except a few of Talbott and Brown's 40 patients are reported sufficiently helped by this regime to be able to live relatively normal lives, but cure is not claimed in any case. Walsh and Adson (1940) were not impressed with the record of the Furstenberg treatment in their 128 patients, they therefore turned to high potassium feeding—using 9 Gm of potassium nitrate daily instead of the potassium chloride of Talbott and Brown—in conjunction with a low sodium diet. It is not evident from their data that superior results were obtained with this régime.

Low Sodium Diet—Avoid all of the following: all salt meats and fish and bread, crackers and butter prepared with salt, carrots, clams, condensed milk, raisins, caviar, cowpens, olives, spinach, cheese, endive, oysters. Take the following no more than twice weekly: lima beans, beets, buttermilk, cantaloupe, cauliflower, celery, chard, dried coconut, dried currants, dates, figs, horseradish, kohlrabi, limes, muskmelons, peanuts, peaches, mustard, pumpkin, radishes, rutabagas, strawberries, turnips, turnip tops, watercress. Of course all food is to be prepared and served without salt.

Histamine—Horton (1911), of the Mayo Clinic, injects histamine intravenously, the treatment is empirical but in his hands has given satisfaction. At the time of his last report he had given 1272 injections without any untoward effects. Dosage and method: 1 mg of histamine base is added to 250 cc of physiological saline solution and this quantity then introduced intravenously during about one and one-half hours (50 to 60 drops per minute). All of Horton's 49 patients have obtained prompt relief from vertigo, nausea and vomiting, less than half obtained improvement in tinnitus. Of these patients, 25 had previously undergone some form of Furstenberg treatment (see above) with some degree of palliative effect, 'but the fact that they returned to the clinic for additional treatment indicated that they were not satisfied with the improvement. Some had received no benefit.'

Some patients seem to get along for months with only the one injection or a few such injections in daily succession in the beginning. For maintenance, Horton suggests 0.1 to 0.2 mg of histamine base subcutaneously two to four times a week, but not much experience with this maintenance dosage has been reported as yet.

Vitamins—Atkinson (1941) has used thiamme hydrochloride and nicotinic acid together in a small number of cases and seems to feel that the results are good enough to make one feel hopeful that something can be worked out on this basis

Surgery—It is almost universally conceded, I believe, that Ménière's disease can be permanently cured by division of the auditory nerve. In the hands of a specialist in this procedure the operative risk is exceedingly low. Dandy (1941) reports that he has performed 401 operations, with 1 death—the 358th case—due to meningitis. The operation is usually performed under a combination of local and basal anesthetics.

MYASTHENIA GRAVIS

This disease occurs usually in early middle age, as often in women as in men, and is characterized outstandingly by excessive fatigability of the muscles, especially those of the face, throat and neck, so that the eyes cannot be opened, there is difficulty in speaking, chewing and swallowing, and the head may roll about loosely. As the disease advances no amount of rest affords sufficient access of strength to break through the paralyses, but actual muscular atrophy is rare and the central nervous system does not really seem to be involved, though the entity is most conveniently studied among the diseases of this system. There are remissions in the course of myasthenia, but ultimately, after months or years, the patient becomes permanently bedridden and dies from exhaustion or pneumonia. The etiology of the disease is still unknown and in its early stages it is not always easily differentiated from neurotic disturbances, the ergograph and prostigmin tests are, however, valuable diagnostic aids. Blalock *et al* (1939) collected from the literature 53 proved instances of myasthenia gravis associated with abnormalities of the thymus, this being about one half the cases of the disease in which postmortem examinations or the findings at operation have been reported. Milhorat and Wolff (1938) conclude as a result of extensive studies that the fundamental metabolic disturbances in this disease are not centered in the metabolism of creatinine and creatine. Hereditary transmission or familial incidence have not been conclusively shown.

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Boothby (1936) summarizing the study of 82 patients at the Mayo Clinic, approximately 50 per cent of whom had improved sufficiently to return to full or half time work, described the treatment as consisting of 2 parts: first, educating the patient, and second, the use of drugs.

Educating the Patient—Instruction should include (a) information that in some instances the disease apparently becomes self limited and that if the patient takes excellent care of himself he may survive into a period of comparative well being, (b) instruction how to conserve strength for eating and swallowing and not to waste it in talking, (c) training in the passage of

a Rehfuess tube through the nose into the stomach for the administration of fluids and food

Prostigmin—In 1934, Walker reported the successful use of physostigmine in a patient in whom she had tried the drug because of the partial resemblance of myasthenia to mild curare poisoning, physostigmine being known as an antagonist in the latter condition. When prostigmin, an analogue of physostigmine asserted to have less pupil and accommodation fixing effect on the eye and less depressing effect on the heart, was introduced shortly thereafter, she also reported the successful use of this drug in a single case. Shortly, Pritchard (1935), and Laurent (1935), each reported effective use in 7 cases, and the wide employment of the drug began. The mechanism of the action is still unexplained, for the assumption that the drug inhibits cholinesterase activity of an excessive degree remains gratuitous since available evidence fails to establish firmly any departure from the normal esterase values in the disease. However, a large number of reports have accumulated to show that prostigmin is very effective in quickly causing partial disappearance of the typical symptoms. The usual method of using the drug in treatment in the beginning was to give from 3 to 5 cc of a 1:2000 solution (containing from 1.5–2.5 mg) of prostigmin methylsalicylate combined with 1/100 grain (0.0006 Gm) of atropine sulfate, intramuscularly once daily. Improvement begins within three to five minutes, is maximal at about thirty minutes, and gradually subsides in from three to five hours. Thus the patient, though he experiences a brief period of release from his symptoms is not really rehabilitated by the drug. Furthermore, nausea and vomiting and abdominal cramps, together with uncomfortable eye sensations and a feeling of faintness often accompany the improvement in muscle power. To obviate these objectionable features of the treatment, Winkelman and Moore (1937) proposed the injection of only 1 cc of the solution without atropine, three times daily, results were very satisfactory in their 6 cases in that muscle power was prolonged during the patient's waking and active hours and there were no symptoms of overaction. Everts (1936) proposed the oral administration of the drug giving three times daily $\frac{1}{2}$ grain (30 mg) dissolved in 3 drachms (12 cc) of water. This is the method of administration now most often employed, but experience has shown that dosage must be highly individualized. Viets and Schwab (1939) found in the study of their 44 patients that the more seriously affected individuals—those with dysphagia and dysarthria as presenting symptoms—required as much as 10 to 20 of the commercially available 15 mg pills in order to obtain the maximum effect, whereas other patients required only a few 7.5 mg doses widely spaced throughout the day. Once the proper dosage is found it seems that increased tolerance or evidences of cumulative action are not seen.

Other Drugs—Minot *et al* in 1939 reported useful effects in 5 of 7 patients in whom *guanidine hydrochloride* was given either alone or to supplement prostigmin. They give the drug either intravenously in 2 per cent solution or orally in capsules, finding 10 mg a safe and adequate test dose. Total daily dosage and spacing has to be developed in each case individually. Gastro-intestinal symptoms seem to serve as a warning that tolerance has been exceeded. In 1941, Dodd *et al* of the same group of workers stated that of the 21 cases reported to them by other physicians, 4 had been considered markedly benefited by guanidine. Viets and Schwab (1939) found that

guanidine increased the effectiveness of prostigmin in 8 of 25 cases in which it was tried. In 1935, Laurent and Walther introduced the use of *potassium chloride*. Viets and Schwab used this drug in amounts of 20 Gm. in 25 per cent solution by mouth daily as supplementary medication in 15 prostigmin-treated cases, in 10 it seemed that decided benefit resulted. *Ephedrine sulfate* and *benzedrine sulfate* have also been used in connection with prostigmin. *Glycine (aminoacetic acid)* does not seem to have proved satisfactory despite earlier favorable reports, Viets and Schwab tried it unsuccessfully in 17 cases.

Surgery—In 1939, Blalock *et al.* reported the removal of a tumor from the thymic region with greatly improved status for the three years preceding the report. In 1941, this same group reported operations performed in 5 patients with the deliberate purpose of removing all the thymic tissue by complete exploration of the mediastinum, the early results at the time of their report were encouraging in 3 of the 5 cases.

MIGRAINE

Migraine is the name applied to a certain type of periodic headache that is associated with visual, gastro-intestinal and to some extent, psychic disturbances. The individual who suffers from this disease is usually made aware of the approach of an attack by several days of malaise, perhaps accompanied by vague or definite gastro-intestinal symptoms, or the attack may come on more suddenly following a period of one or more hours of exceptional well-being, or—and this is not infrequently the case—the patient may recognize a night of more than usually sound and refreshing sleep as a warning signal. In most cases the headache is ushered in by visual disturbances, these may be of the nature of flashes of light, or of wriggling threads of light that pass across the field of vision, or of definite loss of visual acuity, and they may disappear before the onset of the headache or persist for some time after the pain begins. If pain is confined to one side of the head these visual phenomena are usually observed on the affected side only. The pain itself is most intense, and usually, though by no means always confined to one side of the head. Occasionally asymmetrical sweating accompanies the headache. During the attack, which lasts from a few hours to several days, the patient is sometimes more depressed or confused than can be easily accounted for by the distraught state induced by the pain. In about 50 per cent of cases nausea and vomiting occur at the height of the attack.

Migraine usually appears in the early decades of life and tends to diminish in frequency and severity, and often to disappear entirely, as senescence approaches, sometimes it disappears at puberty and returns at the climacteric. It often is absent during gestation, and may disappear for a long period after one of the acute infectious diseases. Nothing is known definitely regarding the cause of this strange malady, though the tendency is known to be almost certainly hereditary. The similarity between migraine and the recognized allergic group—hay fever, asthma, urticaria, angioneurotic edema, food allergy, etc.—has caused the suggestion to be made that it is truly a sen-

sitization disease. Some observers have also placed it among the endocrine disturbances as a point of departure in their studies. That migraine and epilepsy are transmitted from generation to generation as an expression of the same underlying factor in the germ plasma and that an individual with migraine is more likely to produce epileptic offspring than is an epileptic has been suggested by some of the observations. The coexistence of migraine and epilepsy is not significantly high, but momentary seizures much resembling *petit mal* sometimes alternate with and may even replace the migraine attacks as age advances. Riley *et al* (1935) find that routine laboratory investigations do not supply any information of diagnostic value. Von Storch and Merritt (1935) find no consistent deviations from the normal in spinal fluid pressure. Hunt's (1933) reinvestigation by newer methods of the old idea that migraine has something to do with biliary disturbance forced him to conclude that at least local disease or dysfunction of the gallbladder is not the cause of the attacks. Solomon's (1936) investigation indicates that migraine is not caused by a general sympathetic dysfunction. Schumacher and Wolff's (1941) interesting studies indicate the possibility that the pre-headache prodromata follow occlusive vasoconstriction of cerebral arteries whereas the headache itself results from dilation and distention chiefly of branches of the external carotid arteries. The migrainous headache must be differentiated from headache occurring in hypertension and in nephritis with retention, also from the toxic headache of excessive alcohol and tobacco indulgence, the headache of eyestrain and of nasal sinusitis, the bandlike headache which occurs in some of the psychoneuroses, the headache associated with arthritis of the cervical spine, the headache caused by intracranial lesions and by syphilis and the headache which Horton (1941) differentiates as 'histaminic cephalgia'.

Women are the victims of migraine somewhat more often than men or at least they more often have a severe form of the malady and the upper social strata are said to be more frequently afflicted than the lower. The variations in racial incidence are not known to me.

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Hygienic Measures—Most patients believe that the smoother and more even the tenor of their life, especially in the particulars of regularity in sleep and the eating of meals, the freer they remain from attacks, some, indeed, are even able to state with positiveness that a certain type of emotional or even physical indulgence will invariably induce the headache. Something of truth there must be in this, but I think its importance is exaggerated by many individuals for the greatest success in regulating these matters often results in little or no decrease in either frequency or severity of the seizures. The elimination of foci of chronic infection is sometimes rewarded by a remission of many months but almost invariably the attacks return after a while though they are oftentimes permanently lessened in severity. Many a migraine patient is addicted to the habit of taking 'a brisk saline purge' at the first hint of the prodromata, but I do not think it is apparent that he is much helped thereby.

Symptomatic Measures During the Attack—Rest in bed is nearly always self-imposed by sufferers from this disease, since it markedly lessens the throbbing of the head and of course decreases the bodily movements that

so often give rise to added quirks of pain. Darkening of the room and the use of cold compresses are also helpful measures. In mild cases, any of the sedative drugs (for a list and dosage, see *Insomnia*) may be employed, phenobarbital (luminal) being latterly preferred. In severe attacks, prohibitive doses would have to be used in order to bring about any reduction in the suffering. Better results follow the use of the analgesics in mild cases, though their effectiveness seems to be much greater when the attack is beginning to wear off than when it is at its height. Aspirin (acetylsalicylic acid), in a dose of 5 to 15 grains (0.3–1 Gm.) at intervals of three hours for 4 or 5 doses is often used, but it sometimes serves only to make the patient more uncomfortable by reason of the perspiring induced. A capsule of pyramidon (amido-pyridine) and caffeine citrate, 5 grains (0.3 Gm.) of the former and 2 grains (0.13 Gm.) of the latter, three or four times during the twenty-four hours, is effective in some cases, but one should be definitely aware of the danger of inducing agranulocytosis with this drug—personally, I feel that its use is probably no longer justified. Five grains (0.3 Gm.) of phenacetin (acet-phenetidine), or 3 grains (0.2 Gm.) of acetanilid, may also prove effective, especially when combined with caffeine as above, if used several times at three-hour intervals, larger doses are seldom more effective and are more likely to cause the undesirable side-effects of this group: sweating and chills, gastric disturbances, skin eruptions, renal irritation, methemoglobin cyanosis and collapse. The U.S.P. extract of cannabis (better known as Cannabis indica) formerly enjoyed the reputation of being almost specific when used in a pill containing $\frac{1}{2}$ to $\frac{1}{4}$ grain (0.01–0.015 Gm.) not to be too often repeated, but has latterly fallen into a probably deserved disrepute. In some cases, codeine sulfate in a single daily dose of $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.) is very effectively employed, but is open to the objections applicable to all the opium series: the locking of the bowel and the production of nausea and a general depression in the metabolic activities. Habit formation, in the sense in which the term is understood in connection with the opiates, need not be feared from the use of codeine. Morphine and dilaudid are, of course, absolutely contraindicated.

Ergotamine Tartrate (Gynergen)—In recent years all of the following have had a more or less satisfactory chance to show what they could do in relieving or preventing attacks, and all have failed to be consistently effective: histamine, epinephrine, ephedrine, mecholyl, estrogenic substance and pituitary follicle stimulating substance, pituitrin, amyl nitrite, calcium gluconate, and trichlorethylene. However, one substance—ergotamine tartrate—apparently has made a very certain place for itself, though it seems to me not impertinent to remark that a healthy skepticism is still in order, migraine being what it is. The work with ergotamine began on the Continent but a number of American reports are now available, the best of these for presentation here is probably that of O'Sullivan (1936), who with her associates made a careful study of the drug's effects at Bellevue Hospital. The following are the significant points: (a) All but 8 of the 97 patients were benefited in the sense of having obtained great relief from the drug during their attacks but there was no effect upon the frequency of attacks. (b) Once the drug had abolished an attack it never failed to do so again if used in adequate dosage. (c) It was not necessary to increase the size of doses with the passage of time. (d) If the patient takes the drug as soon as he is sure

that an attack is on the way the dosage required to check the attack is much smaller than if he delays (e) The time required for effective control varied from fifteen minutes to five hours (f) The drug is preferably given subcutaneously in a trial dose of 0.25 mg, if the control has not been perfect after two or three hours, the dose is repeated, or it is repeated if the attack returns after eight to twelve hours. In those instances in which repetition was necessary, 0.5 mg is given initially in subsequent attacks, more than this in any attack is rarely needed, 0.75 mg having been used only three times (g) It is most important that the patient lie down for one or two hours after medication, not only to assist it but also to diminish the symptoms of overaction of the drug, which occur in many individuals: nausea, vomiting, muscle pains and weakness of the legs, stiffness of joints, a sense of constriction in the throat, and of heaviness in the chest, and burning and tingling of the fingers and toes. A hypodermic injection of atropine sulfate, 1/100 grain (0.0006 Gm), will check the gastro intestinal distress and 10 cc of calcium gluconate solution intravenously diminishes the muscle pains (h) Response to oral administration of the drug in tablet form is much less satisfactory if nausea and vomiting have already set in it is useless. Five of the 1 mg tablets have been necessary at one time to check an attack even before the appearance of gastro intestinal symptoms, with such heroic dosage no more of the drug should be given for twelve to twenty four hours (i) Use of ergotamine between attacks in the attempt to prevent their recurrence is felt to be unwarranted in view of the very irregular spacing of the attacks such a practice is also very expensive and possibly dangerous.

That ergotamine tartrate is capable of causing extremely severe damage to the organism is shown in the reports of the following (a) In Yater and Cahill's (1930) patient, 19 cc of the standard gynergen solution was administered in one week for control of pruritus associated with jaundice, the gangrene of ergotism which resulted necessitated amputation of both legs (b) The patient of Gould *et al* (1937) already had symptoms of peripheral arterial disease when she was given 4 daily ampule doses (a total of 1 mg) of the drug for relief of pruritus, death a few days later with gangrene of both lower extremities (c) Perlow and Bloch's (1937) patient received 3.5 mg of the drug within a space of ten days for intolerable pruritus. The resultant threatened gangrene was apparently successfully prevented by the use of papaverine hydrochloride $\frac{1}{2}$ gram (0.03 Gm) intravenously or by mouth at intervals varying from four to twenty four hours during five days. Comfort and Erickson's (1939) 2 patients who had severe reactions had also received the drug in the attempt to control pruritus. Von Storch (1938), in reviewing the literature and reporting his own 189 patients treated for one to five years, says that serious ill effects have not followed the use of the drug when it was employed for the treatment of migraine. Nevertheless he says that treatment should be continued with caution in the presence of marked arteriosclerosis, hepatic or renal disease, vitamin C deficiency and hypersensitivity to the drug, contraindications he states to be septic states, especially when associated with intravascular foci and obliterative vascular disease, particularly coronary disease. Carter's (1940) patient developed severe substernal distress and auricular fibrillation following an injection of ergotamine, she had apparently had no preceding cardiovascular disturbances, but he is not certain that the diagnosis of migraine was correct.

Oxygen—Alvarez and Mason (1940) report that in about 78 per cent of 100 cases complete or marked relief occurred upon the inhalation of 100 per cent oxygen. Occasionally a patient relieved at one time would not be relieved at another, in some patients the effects were not so well obtained later as they were when the treatment had been begun. It would hardly seem likely that oxygen inhalation will soon become feasible for the majority of sufferers from migraine, but it is certainly worth pointing out that this type of treatment is not associated with the annoying side actions which so often accompany the use of ergotamine.

Specific Measures—Those who are approaching the migraine problem from the allergy standpoint are reporting a certain degree of success in treating their patients by the various methods of specific desensitization and especially through the use of nonspecific protein therapy and the employment of measures for the diagnosis and treatment of food allergy. It is suggested that the reader study the chapter on allergy.

The possibility of obtaining relief through inducing menopause has been considered by Alvarez (1940), who found that in only 6 out of 42 cases did oophorectomy or hysterectomy, complete or partial, or a sterilizing dose of roentgen rays or radium put a stop to attacks of migraine, in 5 cases the attacks were milder, in 16 they went on unchanged or were better for only a while, and in 15 they became worse.

IDIOPATHIC EPILEPSY

(Paroxysmal Cerebral Dysrhythmia)

Idiopathic or essential epilepsy is a disease characterized by a peculiar type of convulsive seizure and a tendency to mental deterioration. It occurs in individuals with a constitutional inferiority but with no demonstrable pathologic lesion, though physical stigmata too numerous to list here are often noted. In the majority of instances the onset of the attacks occurs before the twentieth year, in more than half before the fifteenth, but the time of appearance of the ultimate terminal dementia is very variable. In many cases the imminence of a convulsion is heralded by a warning visual, auditory, or other type of fleeting aura, which is followed, in about 50 per cent of cases, by the sinister epileptic outcry, then follow the sudden loss of consciousness, the defenseless fall, and the moment of pallor, cessation of respiration, and general muscular rigidity of the decerebrate type. Transition into the clonic stage, in which the body jerks rhythmically and violently, may be made suddenly and generally or in a disorderly manner, so that one side remains rigid while the other is already jerking. During this stage which lasts from three to five minutes and subsides slowly, the skin is cyanosed, the pulse is rapid and feeble, the deep reflexes are greatly diminished, the blood pressure is low, the pupils are first constricted and then dilated and usually immobile to light, foam appears on the lips, bestial sounds are made, and the urine or feces may be violently ejected. Following the subsidence of this stage, the patient passes into a deep stupor of several

hours, though in some instances he partially regains consciousness for a few moments and then falls into a more natural type of deep sleep. For a considerable time after awaking from this stupor, the state is either one of dreaminess, irritability, delirium, or mania during which acts of great violence may be committed. This is the classic *grand mal* seizure, the *petit mal* attack consists in only a momentary loss of consciousness, or some other sort of flashing sensory disturbance, without the occurrence of a convulsion and its sequelae. And then there are the cases in which so-called *equivalents* replace a typical convulsive seizure: unexplained outbursts of temper, tantrums, periods of amnesia, sudden irrational and destructive activity, periods of dulness and apathy. The *status epilepticus* is a state of affairs in which one convulsion succeeds another so rapidly that the patient practically never recovers consciousness, he presents all the signs of profound intoxication and usually dies from heart failure or pulmonary edema. In rare instances only 1 or 2 or 3 attacks, with many years between, are experienced throughout a long lifetime, evidence is accumulating to show, however, that in most cases of epilepsy the seizures follow various rhythmic patterns too complex for analysis here.

Between attacks the epileptic is a disagreeable antisocial psychopath who is gloomy, irritable, suspicious, defensive, boastful and deceitful to cover his emotional poverty, violent, self-centered and uncomprehending. At all times the person with a severe case of this disease is a dangerous individual, those more mildly afflicted as to number and severity of fits particularly if the symptoms do not appear until well on toward or into adulthood, suffer very much less mental deterioration—indeed, Barnes and Tetterman (1938) feel that the personality problems of the epileptic are often due to the social and psychologic reactions to his disease rather than to any change in intelligence. Paskind and Brown (1939) say that we take eventual mental deterioration entirely too much for granted in all cases merely because it frequently occurs in advanced committed cases.

Epilepsy was recognized as an entity in very ancient times. Sudboff interpreted the concept *bennu*, in the tablets of King Assurbanipal of Assyria (668-626 B.C.), as epilepsy, and the description of the disease written by Hippocrates (460-370 B.C.) would almost suffice for any present-day text book. In the Middle Ages it was customary to include epilepsy with the diseases then recognized to be contagious—bubonic plague, tuberculosis, anthrax, scabies, erysipelas, trachoma and leprosy—and to ban the afflicted from the cities, or at least not to permit them to sell food and drink. At the present time, we are convinced that the disease is not infectious and certain that heredity plays a part in its causation, but otherwise the etiology remains unknown and a satisfactory classification of the various types is still to be proposed. The claims of those who argue for the inclusion of epilepsy among the diseases of allergy are interesting, Harris has shown that some cases are associated with a state of hypoglycemia, in a very small proportion of the cases some demonstrable brain lesion is the sole cause of the seizures; now and then seizures occur as a part of a frank endocrinopathy, undoubtedly cysticercosis of the brain is responsible for numerous cases in the Far East, but the most significant advance in the knowledge of idiopathic epilepsy that has been made in all its long history is the recent recognition, largely as a result of the studies of Lennox and his associates at Harvard, that in about

95 per cent of patients there are abnormalities in the electroencephalogram which show up even during an asymptomatic period, this is the evidence indicating that seizures are accompanied by profound alterations in the rate and force of the electrical pulsations of the cortex, which warrants us in applying to epilepsy the new title "paroxysmal cerebral dysrhythmia." It is estimated that there are in the United States 500 000 frank cases of the disease *etc.*, about as many as there are of diabetes and of active tuberculosis.

THERAPY

Hygienic Measures—If essential epilepsy is incurable, and it probably is in the present stage of our knowledge, nevertheless very much can be done for these sufferers. But the physician who merely writes a prescription for one of the anticonvulsant drugs, makes a few vague remarks as to dietary restrictions, suggests that the family make life easy for the patient, and then takes no vigorous and persistent subsequent steps to see that these measures are instituted to the fullest advantage of the patient, is shirking his hounden duty, for no individual is more prone to suit a treatment to his own convenience or whims, and finally to stop it altogether, than the epileptic.

It is probably true that the rehabilitation of the patient's hygiene by which I mean his readjustment to his environment, is the single most important element in the treatment. These individuals are defectively equipped to cope with a social existence, and therefore must be especially protected. Fatigue is their greatest enemy, fatigue of mind, body or emotions, therefore they must be placed in such surroundings that they may perform light work (preferably remunerative so long as their mentality is alert to the significant facts of their plight), be much out of doors, bathe often and keep the skin in good condition, eat nourishing food but not much at a time, have alcohol, tobacco, and to a large extent tea and coffee withheld from them, and be encouraged not by maudlin sympathy but by a rational optimism to enjoy the many advantages of life that may be theirs despite their handicap. For most epileptics, of whatever station in life, these desiderata can perhaps be best approximated in either a public or private institution provided it is well conducted, but in many cases the readjustment is better accomplished without too radical a change in environment. Certain it is that to stop at once the education of a child or youth as soon as the diagnosis is made is not justified unless the case be hopelessly severe from the beginning for many of these children are precocious and will absorb much in their early years that will help to sustain them at a later time, furthermore no one can predict with certainty that a mild case may not continue to be so always under proper care.

The Bromides—The bromide salts were introduced into the treatment of epilepsy in 1858 and enjoyed an undisturbed and deserved preference over all other remedies until their position was challenged by phenobarbital and more recently dilantin. Bromides have now been almost abandoned but it is well to bear in mind that this abandonment has not occurred because they were not effective. As a matter of fact there are not available any fully controlled large scale studies of these drugs under the conditions in which the general practitioner employs them, *etc.*, in the attempt to keep moderately afflicted epileptics economically productive and socially adjusted.

Perhaps the nearest approach to such a desirable study is that of Lennox (1940) who tabulates the results in 766 extramural patients who had taken phenobarbital and 289 who had taken bromides. Of the phenobarbital group 65 per cent reported improvement and of the bromide group 53 per cent improvement in mentality was reported by 80 and 26 per cent respectively. These differences are not of statistical significance considering the great disparity in numbers of patients in the two groups. I am not wishing to make out a case for the superiority of the bromides to phenobarbital or even contending that they are probably quite as good but I think that from the standpoint of accuracy it should be stated that there were other reasons than ineffectiveness for turning away from them when opportunity presented. These reasons are that the bromides not infrequently obtain their good effect at the price of sluggishness and apathy that the skin rashes often induced by them if not serious in themselves are an added embarrassment to an individual already prodigiously handicapped they often cause gastric disturbances and they are more expensive than phenobarbital. As is the case with the other drugs also *grand mal* is more effectively treated by the bromides than is *petit mal*.

There is a firmly entrenched clinical impression that mixtures of several bromide salts are superior to any one alone so the Erlenmeyer mixture (1 part each of potassium and ammonium bromide and 2 parts of sodium bromide) has been much used as also the elixir of three bromides of the National Formulary which is a colored and flavored preparation containing in 1 fluidrachm $4\frac{1}{2}$ grains (0.3 Gm) each of sodium potassium and ammonium bromide. It is highly probable that full anticonvulsant action can be obtained with either sodium or potassium bromide alone. Average adult dosage is 15 grains (1 Gm) three times daily but careful study is required to determine by adjustment up or down from this dosage the amount required in a given case. Dosage is reduced for children roughly in proportion to their weight. Bromide therapy is more effective if the diet is kept relatively salt free but resort to this measure is usually necessary only in very resistant cases.

The following prescription is acceptable for disguising the bromide taste

Rj Sodium bromide	℥i	30 0
Water	℥i	30 0
Syrup of glycyrrhiza to make	℥iv	120 0
Label: 1 teaspoonful in water or milk three times daily		
(Note: 1 teaspoonful 15 grains, 1 Gm of sodium bromide)		

Bromide overdosage is evidenced by foul breath and coated tongue any one of the characteristic skin lesions especially sudden and extensive acne lethargy and mental dulness slurring of speech slow pulse and a staggering gait. Treatment consists in stopping the administration of the bromide and administering sodium chloride in equal or larger amounts to hasten bromide elimination. Toenhart (1935) confirmed by others has shown that continuous aspiration of the stomach materially hastens bromide elimination under these circumstances saline should be administered intravenously. The reported successful employment of adrenal cortical extract is not likely to stand the test of time as it seems to be scientifically unsound indeed it has already been soundly criticized for this reason and also on the basis of actual failure to confirm the clinical findings.

Phenobarbital—In recent years this drug has largely replaced the bromides for the reasons previously stated (see Bromides). Phenobarbital is insoluble and is therefore given in tablets or in powdered form in capsules. Peterman (1935) used the following dosage in children: two to five years, $\frac{1}{2}$ grain (0.08 Gm) once or twice daily; five to ten years, $\frac{3}{4}$ grain (0.045 Gm) two or three times daily; ten to fifteen years, $1\frac{1}{2}$ grains (0.1 Gm) two to four times daily. In resistant cases in adults, $2\frac{1}{2}$ grains (0.2 Gm) may be given three or rarely four times daily for a limited period, but many adults need no more than $1\frac{1}{2}$ or 2 grains (0.1 or 0.13 Gm) daily. Lennox (1940) has pointed out that $\frac{3}{4}$ grain tablets cost five times as much as $1\frac{1}{2}$ grain tablets, it should be known to everyone by this time that phenobarbital bought under the trade name of 'luminal' is more expensive than the official drug. The elixir of phenobarbital of the National Formulary contains $\frac{1}{2}$ grain (0.015 Gm) in a teaspoonful (actually in 4 cc).

Phenobarbital sodium, the soluble form of the drug, is used when it is necessary to administer the drug hypodermically. It is customary to prepare a 20 per cent solution in boiled and cooled distilled water, 15 minims (1 cc) of this solution contain 3 grains (0.2 Gm) of the drug. The dose of phenobarbital sodium is 10 per cent greater than that of phenobarbital.

Many physicians have noted that the bromides seem to lose their effect after the unsuccessful administration of phenobarbital. This is a serious fact, for if the individual has been doing fairly well on the bromides and becomes worse on phenobarbital, we have then severely crippled our therapy. Graiker writes that in cases not responding well to phenobarbital, he combines bromide with the phenobarbital and by gradually lessening the amount of phenobarbital and increasing the amount of bromide, he believes that he obtains better success upon his full return to the latter drug. Another serious feature of phenobarbital medication is the fact that, whether the administration is successful or not, stopping the drug suddenly is almost always followed by an increase in the incidence and severity of the attacks above that reached before phenobarbital had been started. However, Fox, in England, has recorded his observation that a second phenobarbital attempt sometimes succeeds after an initial failure.

The following by effects of phenobarbital administration are infrequent but should always be borne in mind as possibilities, since they probably occur as often following small as large doses: (a) a dermatitis resembling that of measles or scarlet fever though it is usually very itchy, (a few cases of fatal exfoliative dermatitis are on record), Peterman (1931) has also reported an eruption exactly simulating bromoderma which followed a healed true bromoderma on the same sites, (b) a peculiar eruption upon the tongue, (c) states of apathy, mental sluggishness and slow speech much resembling those seen as a result of bromide therapy, (d) great muscular weakness, (e) extreme irritability, sometimes leading to violence, (f) a state of intoxication that may be mistaken for acute alcoholism, (g) and occasionally subacute and chronic epigastric pains.

None of the other barbiturates has been nearly so effective as phenobarbital in the treatment of epilepsy, but this drug, like the bromides, is much more effective in *grand mal* than in *petit mal*. Southerland (1940) has reported a group of institutionalized patients who had fewer seizures when given 1 gram of phenobarbital in the morning and 30 grains of bromide in the after

noon than when given 1 grain of phenobarbital alone twice daily. A number of observers have found it advisable under some circumstances to combine dilantin with phenobarbital (see Dilantin). Cohen *et al* (1940) reported the elimination of some of the undesirable sedative action of phenobarbital by the concomitant use of 5 to 25 mg. of benzedrine sulfate daily, but Stone *et al* (1940) were unable to confirm this finding. Loscalzo (1938) has asserted that belladonna alkaloids can replace a part of the phenobarbital, but this proposition needs extensive investigation before one is justified in accepting it.

Just how long the patient may take phenobarbital without being harmed is not known, but Smmerfeld Ziskind and Ziskind's study of 100 noninstitutionalized patients indicates that as much as $1\frac{1}{2}$ grains (0.1 Gm.) two or three times daily may be taken for at least two years (the length of their study) without resultant deterioration of the intellect.

Dilantin (Epanutin)—Since 1938 when Merritt and Putnam at Harvard introduced dilantin it has had extensive trial. The drug which is sodium diphenyl hydantoinate, is analogous to the barbiturates in its chemical nature, being a derivative of glycolyl urea instead of malonyl urea. In Merritt and Putnam's 1940 report on 267 patients refractory to other forms of therapy (principally phenobarbital) they find the drug effective in reducing or controlling convulsive seizures in 227 instances over periods varying from two months to two years. Greatest effectiveness was obtained in psychic equivalent attacks, next in *grand mal* and least in *petit mal*, the effect upon psychic equivalent attacks is particularly noteworthy because neither of the two older drugs have much influence upon this type of epilepsy. The findings of the Harvard group have been substantially confirmed by a number of workers, for example Kimball and Horin (1939), Hodgson and Reese (1939) and Lettermann (1940) in the United States and Blair *et al* (1939) in England to mention only a few. In addition to what appears to be a somewhat greater ability to reduce the incidence of seizures than is possessed by the older drugs, dilantin has the great advantage of not acting as a sedative, in fact it is the general impression that many patients are mentally brighter while taking the drug. Ross and Jackson's (1940) exact study of this latter point did not reveal any significant influence on intelligence ratings, but about half their patients showed no improvement in conduct, and performance ratings were raised appreciably in a small percentage.

On the credit side, therefore, the record is very fine, probably greater efficacy against *grand mal* than phenobarbital, which is itself considered better than the bromides, certainly greater efficacy against psychic equivalents, lack of stupefying or even sedative properties, and possibly an alteration in the epileptic temperament toward the better in some instances. Unfortunately, however, as in all matters in this best of possible worlds there is another side to this picture. For one thing the drug is much more expensive than phenobarbital, and therefore unless its superiority is definitely established with the passage of time this will remain a serious drawback to its general use. Another thing is that *petit mal* attacks are often more frequent under dilantin (Lennox, 1940). Then there is the matter of the drug's toxicity. Pratt (1939) has reported toxic reaction in 73 per cent of 52 patients, the most frequent in occurrence being subjective tremulousness with a feeling of apprehension and tension, tremors, dizziness, ataxia, nausea and sometimes vomiting, burning sensation in the eyes, diplopia, and blurring

of vision. Psychotic reactions occurred in 5 cases, Peterman (1942) finds these reactions occurring quite frequently in children and constituting a serious objection to the use of the drug. Kimball and Horan (1939) found peculiar hyperplastic reactions in the gums in about half their patients, so too did Pratt and a number of other observers in the United States, strangely, in England, as pointed out by Blair (1940), this reaction occurs extremely rarely. Merritt and Foster (1940) have confirmed in man Gruhitz's earlier finding in animals that this gum reaction is not caused by a drug induced vitamin C deficiency, though at times the appearance of the gums does bear some superficial resemblance to the picture seen in scurvy. Less frequently occurring reactions are toxic dermatitis (exfoliative dermatitis has been only rarely observed), hirsutism in adolescent girls, nosebleed, purpura, McCartan and Carson (1939) report a slight depressant effect on hemopoiesis in all of their 20 cases, but Merritt and Putnam (1939) do not find such bone marrow effects.

The occurrence of any of the above toxic effects of course calls for reduction or omission of the drug for awhile, but it is not always easy to do this without throwing the patient into a period of heightened number of seizures, most men now resume phenobarbital administration as soon as it becomes apparent that dilantin must be omitted. The danger to life of dilantin overdosage seems to be very slight. Aring and Rosenbaum (1941) report a patient who upon four occasions ingested 60, 90, 105 and 57 grains (4, 6, 6.8 and 3.8 Gm), respectively, the chief symptoms each time were exhilaration, light-headedness, dizziness, nausea and vomiting, headache, staggering diplopia, nystagmus, difficulty in converging the eyes, pupillary abnormalities, ataxia, tremor, and changes in reflexes. Robinson's (1940) patient, who ingested 67½ grains (4.5 Gm), was in coma for a few hours and then suddenly regained complete consciousness.

Dosage—Merritt and Putnam, whose use of the drug has set the standard, find regulation of the dosage not difficult in patients who are having several or many attacks weekly. 1½ grains (0.1 Gm) are given in capsule form, preferably with or after meals, three times daily and increased if necessary in increments of 1½ grains (0.1 Gm) every ten days or two weeks until relief is obtained or toxic symptoms appear, in most cases after the control level is reached this must be maintained without reduction. Patients who have relatively infrequent attacks are often more difficult to treat but they are frequently given 6 to 7½ grains (0.4 to 0.5 Gm) daily in the attempt to prevent attacks which might interfere with their occupation or education. All observers agree that the change over from phenobarbital to dilantin must be made with extreme caution. Fetterman's (1940) method will serve as an example, it being a scheme which depends on the gradual reduction of phenobarbital over a period of three to four or five weeks with the simultaneous replacement by dilantin in gradually increasing amounts. "If a patient has been receiving, let us say, three tablets of phenobarbital daily, it is a good rule to replace one tablet by one capsule of dilantin sodium daily during the first week and then, during the second week, to replace two of the phenobarbital doses by two capsules of the other drug. During the third week, if there are no attacks, one may replace the phenobarbital entirely, but it is safer to continue with at least one dose of phenobarbital plus three capsules of dilantin sodium. Should attacks continue and no complex side actions develop, the dose of dilantin may be increased to four or five capsules daily for an adult."

Combination with Phenobarbital—A number of men are finding that cases more or less recalcitrant to either drug will frequently do much better on a combination of the two, typical reports are those of Pratt (1939), Cohen *et al* (1940), and Robinson and Osgood (1940). Of course the proper dosage combination must be developed through careful trials in each case.

The Ketogenic Diet—Fasting as a dietary measure in the treatment of epilepsy was first suggested by Guelpa and Marie, in 1910, but it was not until 1921 that Geyelin applied the suggestion in practice. Most of his children were freed from seizures during the period of fasting which produced ketosis, but the attacks returned sooner or later after the resumption of a normal diet. Repeated periods of fasting were thus shown to be impracticable in the maintenance of ketosis. However, in the same year, Wilder while working with high fat diets in the treatment of diabetes mellitus, suggested their use in the treatment of epilepsy as a means of producing ketosis and still supplying adequate food. This marked the beginning of the ketogenic diet, so called because the ketogenic factors outweigh the anti-ketogenic factors, but evidence has been accumulating to the effect that it is not the disturbance in the acid base balance *per se* (i.e., not any sort of sedative, anticonvulsant effect of the ketone bodies) but rather the dehydrating effect of starvation, or of a ketogenic diet, which is important in bringing symptomatic relief—an idea originally suggested by both McQuarrie and Fay in 1929. The hypothesis is that in epilepsy there is an increased production of cerebrospinal fluid in the nonextensible cerebrospinal space, that this increased pressure is associated with the convulsions in some causative or provocative relation, and that the effect of the treatment is the result of the removal of this surplus of extracellular fluid. Clinical attempts to test the hypothesis by simple reduction of the allowed fluids to a very low point have not been productive of satisfactory results in the hands of Fetterman and Kumm (1933), and Wilson and Lumberger (1933). The study of Greville and Jones (1940) seems to reveal that retention of body water does not by any means invariably precede a seizure, however, Ziskind *et al* (1939) are often able to precipitate seizures by the administration of excessive quantities of water, a procedure which is sometimes employed as a diagnostic aid. Despite the conflicting evidence a number of men believe that dehydration is of value in conjunction with both drug therapy and the ketogenic diet.

The new method of attack upon this ancient enemy was grasped with avidity by the pediatricians, so that the earliest reports were of its results in the treatment of children. In 1932, Peterman, of Milwaukee, reported a series of 85 patients, 42.5 per cent of whom had been free of convulsions for from six months to three and one-half years, of the 267 children in whom adequate trial of the diet was made at the Mayo Clinic since 1922. Helmholz and Goldstein (1937) report that 31 per cent were freed from attacks for at least one year. In both series, as in the experience of other observers, a considerable number of patients was much helped but not completely relieved of attacks. Amoss (1938) reports a case in which the diet increased the number of the seizures and also their duration and severity. Wilkins (1937), at Johns Hopkins, feels unable to evaluate scientifically the results obtained with the diet but believes the successes sometimes had in cases of a type most unresponsive to other therapeutic measures justify its trial whenever attacks are not controlled by sedatives. In his selection of patients

Peterman excludes all with any evidence of organic lesions and those who are already sufficiently advanced in the disease to have reached the stage of mental deterioration

In 1930, Barboraka, who had carried the diet over into the treatment of adults, reported complete control of attacks in 12 per cent of 100 patients though again as in children, considerably more than this proportion obtained some help. Observers are agreed that upon the whole the treatment is much less effective in adults than in children

Diet for Children—After a preliminary fast of ten to fourteen days, with the patient in bed, during which the daily allowance is only 8 ounces (250 cc) orange juice, 16 ounces (500 cc) diabetic broth, 6 or 8 bran wafers such as Cellu bran and 13 ounces (400 cc) water, the ketogenic diet is begun abruptly. For the general practitioner who has not an expert dietitian at his elbow, it seems to me that the best that can be done is to follow the general plan recommended by Peterman (a) a definite daily regimen to include a long nap and a long sleep, meals at regular hours and a daily bowel movement, (b) restricted carbohydrate and protein and a high fat diet, (c) fluid restriction to a minimum, at least to 600 or 800 cc daily and less if convulsions continue, (d) phenobarbital in large enough doses to control any seizures which may occur after or until the above procedures are established

He offers the following sample menus

SUGGESTED KETOGENIC MENUS FOR CHILDREN

(Modified from Peterman and Clausen, Milwaukee Children's Hospital)

Five Years of Age

Breakfast

30 Gm sliced orange
13 butter
1 egg—omelet
100 Gm 30 per cent cream
May have Cellu bran breakfast food

Dinner

50 Gm spinach
13 butter
20 " scraped beef patty
50 " cream for drinking
50 " cream—ice cream { WL p cream
and flavor
with $\frac{1}{2}$ tea
spoonful vanilla,
 $\frac{1}{2}$ gr saccharin

May have bran wafers

Supper

Celery soup { 50 Gm cream
20 celery
10 " butter
50 Gm asparagus
6 butter
50 cream
May have D Zerta
Fluids—300 Gm
1000 cc — 300 cc = 700 cc, water may be
allowed between meals

Ten Years of Age

Breakfast

30 Gm fresh pineapple
20 butter
1 egg—scramble with cream and butter
100 Gm 30 per cent cream
May have Cellu bran breakfast food

Dinner

50 Gm broiled tomato
26 butter
68 steak with mushrooms (no available
food value in mushrooms)
73 " cream to drink
1 "D Zerta with 25 Gm whip cream

Supper

Vegetable soup { 50 Gm broth
10 celery
10 onion { 40 Gm
10 " carrot { 5% veg
20 " butter
50 Gm raw cabbage with 12 Gm. mayon
naise
20 bacon { 100 Gm cream
100 cream—cocoa { $\frac{1}{2}$ tsp cocoa
 $\frac{1}{2}$ gr saccharin

Fluids—350 Gm.

1000 cc — 350 = 650 cc, water may be
allowed between meals

When the diet is found that will keep the patient free from seizures, which may require increasing the fat to the point of intolerance, it should be maintained four months, then additions of proteim, 10 Gm, are made every two months alternating with additions of carbohydrate of the same amount

Diet for Adults—The trial of this type of therapy for urinary tract infection as well as for epilepsy has led to much simplification in methods, but it is nevertheless still difficult to get patients to persist for long in the treatment. Clark (1936) offers the following simplified diet, with the supplementary instructions that (a) saccharin may be used for sweetening (b) no gum chewing tobacco, cathartics other than liquid petrolatum or bitter cascara, no medicines not prescribed, (c) bran wafers must have no food value, (d) water is allowed in only very moderate amounts, (e) if nauseated omit a meal or two, taking one half glass of tomato juice, one half orange or a glass of sour lemonade

SUGGESTED HIGH FAT KETOGENIC DIET FOR ADULTS (Modified from Clark)

Menu 1 Jan

Include the following foods daily, in the exact amounts specified

Heavy whipping cream	1½ pints (3 cups)
Eggs	6

Any combination of 2 eggs and 1 cup of cream may be used at each meal. Below are three suggestions. If desired some cream may be used between meals with coffee or tea

Breakfast

Scrambled eggs	
Eggs	2
Heavy whipping cream	½ cup
Bran wafers	as desired
Heavy whipping cream	½ cup
Butter	as desired
Coffee or tea	as desired

Lunch

Poached egg	1
Baked custard or custard ice cream	
Egg	1
Heavy whipping cream	1 cup
Water	½ cup
Nutmeg and saccharin	if desired
Bran wafers	as desired
Butter	as desired

Dinner

Egg omelet	
Eggs	2
Heavy whipping cream	½ cup
Bran wafers	as desired
Iced coffee	
Coffee	as desired
Heavy whipping cream	½ cup
Butter	as desired

Nesbit and McDonnell's (1935) type of diet is a clever one, instead of supplying excess fat in a maintenance diet they simply supply a diet so

much below maintenance requirements that the patient achieves ketosis through utilization of his own body fat. The diet has been successful in a large number of patients though ketosis is necessarily slowly achieved with it. Patients do not find it nearly so repugnant as the other type of diet.

SUGGESTED LOW CALORIE, LOW FAT KETOGENIC DIET FOR ADULTS

(Venhal and McDonnell)

Breakfast.

Egg 1
Bacon, 2 long strips
Cream or milk, 1 tablespoonful
5 per cent vegetable $\frac{1}{2}$ cup cooked
Bran wafers as desired*
Butter as desired
Tea or coffee

Luncheon.

2 eggs or 2 ounces of meat or fish or 3 tablespoonfuls of cottage cheese
5 per cent vegetable, $\frac{1}{4}$ cup cooked or $\frac{1}{2}$ cup raw or
5 per cent fruit
Cream or milk, 1 tablespoonful
Bran wafers as desired*
Butter or mayonnaise as desired
Tea or coffee

Dinner the same as luncheon

Sample Meals for Day

Breakfast.

1 egg fried with 2 strips of bacon
 $\frac{1}{2}$ cup of tomato juice
Bran wafer with butter
Coffee with 1 tablespoonful of cream

Luncheon

Cottage cheese 3 tablespoonfuls
 $\frac{1}{2}$ head lettuce with 2 tablespoonfuls of mayonnaise
Bran wafers with butter
Coffee or tea with 1 tablespoonful of cream

Dinner

Steak, 2 ounces
Cooked spinach, $\frac{1}{4}$ cup with butter
Raw celery, 2 stalks
Bran wafer with butter
Coffee or tea with 1 tablespoonful of cream

No sugar is allowed. Chewing gum, chewing tobacco, toothpaste, sweetened cereals and the like are not allowed. Glucose (saccharin) may be used for sweetening. Fruits must be fresh or canned without sugar. Mayonnaise should be made without sugar.

* Bran wafers must have no food value

Treatment of the Attack—In a few individuals with a long aura the use of amyl nitrite, by inhalation from a pearl crushed in the handkerchief, will sometimes abort an attack. During the course of a seizure about the only thing that can be done is to prevent injury insofar as is possible. A spoon or other object should be introduced between the teeth to prevent biting of the tongue, the clothing should be loosened, the mucus removed from the mouth, and the site of such gross injuries as may have been received in the fall protected as much as possible during the clonic period. Nocturnal epileptic attacks often precipitate the patient out of bed unless special safeguards are provided. The promotion of a quick return to consciousness by the use of cerebral stimulants is contraindicated, for such forced recovery from stupor is often obtained at the price of a terrific headache and very prolonged exhaustion.

Treatment of Status Epilepticus—The most usual methods of treating this state are by the use of strong purges, colonic irrigations with cold water, applications of ice to the spine, large doses of bromides, chloral hydrate, morphine or dilaudid, paraldehyde, phenobarbital sodium, and chloroform. Bromides must be used in a large dose of 60 to 80 grains (4-5 Gm.), or

chloral hydrate may be given in the same amount by rectum, morphine or dilaudid in full dose is sometimes combined with either of these drugs Grinker (1929) gives 3 to 5 grains (0.2-0.5 Gm) of phenobarbital sodium intraspinally in 5 to 10 cc of physiologic saline after drainage, intravenous injections of 3 grains (0.2 Gm) every four hours may be made Collier (1928) prefers paraldehyde to any other remedy giving it in a dose up to 8 drachms (52 cc) in an equal quantity of olive oil by rectum, Wechsler (1940) finds 1 cc of the drug injected intravenously the most effective agent he has ever used When a general anesthetic is necessary, chloroform is preferred to ether because of its quicker action Robinson's careful studies at the New Jersey State Village for Epileptics convinced him that chloroform, pushed only to the point of producing complete relaxation, is the best remedy of all Venesection should probably never be practiced unless injection of physiologic saline is made at the same time

During the postconvulsive stupor, it may be necessary to continue the use of anticonvulsants, for these patients are often in a state of motor unrest even after the convulsions have ceased Supportive treatment is most important, alcohol, digitalis, caffeine, as indicated The use of nutritive enemata and fluids by hypodermoclysis or intravenously may be necessary, bearing in mind the great metabolic upheaval that has been experienced by the body Delirium is perhaps best controlled by scopolamine hydrobromide 1/200 to 1/100 gram (0.0003-0.0006 Gm)

Storchheim (1933), feeling that pulmonary edema with consequent or accompanying heart failure was largely responsible for the fatal termination in his 5 patients treated with sedatives or anesthetics turned to the intravenous injection of magnesium sulfate He gave 10 cc of a 25 per cent solution, very slowly and between convulsions, to an adult, repeating once or twice if necessary In 1937, shortly before his untimely death, Storchheim kindly informed me that 20 patients had been treated, all successfully, 1 patient had been brought through 30 attacks of severe status with no more mental deterioration than when first seen five years previously

Miscellaneous Remedies in Epilepsy —The following remedies have had their advocates but have never been employed with anything approaching consistent success erotalin, acetanilid, acetylcholine, sodium borate (borax), protein desensitization, organotherapy, fever therapy, antirabic vaccine, and *Bacillus acidophilus* therapy In connection with the claims that have been made for these agents, it is to be remembered that the epileptic often responds favorably to anything done to or for him, but it is only upon those measures that will produce results under any circumstances and time after time that our hopeful therapy can be based

INSOMNIA

The physiologic condition of sleep, so well known in its gross aspects, is as yet by no means scientifically understood Evidence is accumulating of the existence of a still vaguely mapped-out initiating center in the brain stem, but the exact nature of the functional break which it is assumed to

make between the cerebral cortex and the remainder of the central nervous system remains unknown. Likewise, we have no more than theoretical knowledge of the alterations in tissue balance which provoke activity in this center. That the cortex does play an important role in sleep induction is indicated by the common experience of irresistible somnolence when mental employment becomes very monotonous or boring and it is a noteworthy fact that decorticated dogs sleep excessively. Pavlov was able to induce the state as a conditioned reflex in laboratory animals, while the preliminary preparations usually made by the human before 'going to sleep' indicate an element of this in man also. But the newborn infant sleeps most of its time, and therefore something more than a conditioned reflex, which must be acquired, is at work here.

Recent carefully performed and confirmed studies have shown that in rabbit, dog and human the passage from waking into natural sleep is accompanied by a considerable fall in the calcium level in the peripheral circulation. The corollary showing that calcium rises simultaneously in the brain has not been convincingly made, but injection of calcium into the hypothalamic region of animals induces sleep. The peripheral blood calcium fall occurs also when sleep is induced with drugs, but when a drug acts contrarily and causes excitement (as sometimes in man and frequently in cats), then it does not occur. Thus the intimate relationship of the calcium fall to sleep is plainly shown, but as yet we know nothing of its significance. Formerly certain phenomena accompanying sleep—such as decrease in blood pressure, heart rate, urine and digestive juice secretion—were considered mere reflections of the lowered metabolic state due to relatively complete muscular inactivity, but nowadays we are not entirely pleased with this assumption and are wondering why gastric motility increases, why the pupil constricts though the eye is closed and why the rising CO_2 in the blood fails to prevent respiratory slowing as it would do in the waking state. The chief points of departure in present research are as follows: conditioned reflex, calcium shift, passive anemia of the brain, accumulation of metabolic products acting as sleep-inducing toxins, emptying of the 'bromohormone' out of the pituitary and its reappearance in the gland just before waking, breaking of synaptic connections by withdrawal of dendritic processes, proprioceptor fatigue from muscular action, parasympathetic (sleeping) dominance over the sympathetic (waking) influence in the brain stem centers. There has been denial as well as substantiation of most of the findings to date.

We have no reliable gauge of the optimum amount of sleep for the adult human though it almost certainly varies widely with individuals nor have experimental studies shown convincingly that moderate periods of enforced wakefulness in the healthy are followed consistently by significant disturbances. But since nightly sleep is so absolutely universal and refreshing its failure to occur with satisfactory regularity in otherwise healthy persons always merits investigation while it is age-old clinical experience that sleeplessness in patients already struggling with illness may be a most serious affair. Practically all who are unable to sleep fall into one of three categories: (a) those who experience great difficulty in going to sleep, (b) those who cannot remain asleep long enough to become completely rested, and (c) those who suffer from fitful sleep throughout the night. In a general way sleeplessness of the first sort is due either to excessive excitability in the cortex or

in some of the neuroses, or to the arrival there of excessively strong stimuli as in instances of undue excitement or sorrow or the presence of pain, coughing dyspnea or the discomfort of a feverish state. Experience indicates that insomnia of the second type (inability to remain long asleep) is often associated with inflammatory or degenerative (such as arteriosclerotic) changes in the subcortical (brain stem) centers. The third type of insomnia, "the fidgets" of motor restlessness, is usually due to excessive fatigue or in some instances merely improper sleeping conditions as to bed, noise, temperature, light, etc.

HYPNOTIC DRUGS

Many physical, hygienic and psychotherapeutic measures need to be employed in luring and holding sleep, most of them too obvious to require listing here, but perhaps the mentioning of one or two little 'extra dodges' may not be amiss. One is that there are many more people disturbed by noise than is commonly believed, individuals, that is, who sleep well enough once they sink into the state but who are kept awake long after going to bed by what Horder (1934) aptly describes as "appreciation of the fact that certain noises are needless and preventable." The trick here—and I shall not seek to make Lord Horder responsible for the remedy as well of which indeed he may not approve—is to assure these people that there is ample ground for their peevishness, and that most impressive (one need not add rather hopelessly ineffectual) bodies of citizens are "dealing" with the matter in several countries but that pending the arrival of blessed silence the only feasible thing to do is shut out the horrid jangle—then follows the advice to visit a sporting goods store for the purchase of a pair of the gadgets professional swimmers use to plug their ears while in the water. Thus one supplies sympathy, understanding and a remedy (only of course nowadays some people like to hear the bomb before it has whooshed right into the house!). Many persons are sensitive to light, too. There are black shields with padding for the hollows under the eyes, commercially available, but they quickly grow soiled and easily lose themselves. A black sock, fastened toe to top with a very small safety pin, fits well over the head and is not excessively warm. Then, too, there is the matter of eating. Many individuals cannot sleep if they have recently eaten therefore nearly all people think that late supper-eating is harmful. This is of course not based on fact, and some insomniacs will be actually relaxed by a bit of food taken just before going to bed. And finally, in just this last group especially, in rare instances blood sugar studies will reveal the insomnia as one of the manifestations of hyperinsulinism, dealt with elsewhere in the book.

When drugs must be used we would wish to have at our disposal agents that both quickly and reliably put the patient to sleep (or keep him asleep if early waking is his complaint) without upsetting the stomach or causing a preliminary period of excitement and without dangerously disturbing the cardiovascular or other physiologic functions, furthermore we do not wish to induce habitual dependence upon the drug or to cause cumulative poisoning through slow excretion. These are severe criteria and no hypnotic drug entirely satisfies them. Chief experimental and clinical interest in the hypnotics centers in the following matters. *Chemistry* In a number of instances particularly among the barbiturates, replacement of one or more hydro

carbon groups by others will alter the activity of a drug, but accurate prediction of the hypnotic effectiveness of new synthetic compounds is still impossible. *Site of action and classification* Experimentally it has been shown with fair certainty that chloretone and the barbiturates are brain stem-acting, while the others affect primarily the cortex. This would indicate especial usefulness for chloretone and the barbiturates in maintaining sleep⁹ otherwise induced, while alcohol, chloral hydrate, the bromides, paraldehyde and the bromural-carbromal group had best be used to put the patient to sleep in the beginning. *Choice of drug* From the above it would seem that choice of a drug in each of the two primary types of insomnia would be easy and that an individual suffering both from difficulty in going to sleep and in staying asleep had best be given a drug of each of the two types both in reduced dosage. But unfortunately clinical impression does not entirely substantiate the experimental findings, and we do not have any extensive bedside studies which decisively settle these points. The reasons for this lack of certainty are three. First, there has apparently been great reluctance upon the part of practitioners to experiment with mixtures despite the fact that the only one in common use—the chloral bromides mixture—has amply proved its worth through the years. Second, the immense amount of advertising propaganda by the barbiturate manufacturers has engendered the notion that the drugs of this group can amply replace all others, and hence much time has been spent in comparative studies solely within this group. Third, experimentation with lower animals has yielded much information on the anesthetic properties of these drugs and has shown the relative margins of safety between merely stupefying and surely fatal doses, thus indicating the *probably* admissible dosage range for new compounds, but comparative studies of true hypnotic values must still be made in the human for the reason that the moment of beginning sleep in animals is extremely difficult to determine. Ataxia, complete muscular relaxation, the inability to move away from a probe introduced into the external auditory canal or to resent placing of the body in an abnormal position—these things indicate a depression that has already gone beyond ordinary sleep and are therefore invalid as criteria of hypnotic value. The superiority of any drugs to chloral (preferably in combination with sodium bromide) and barbital in their respective classes has not yet been proved (Grabfield, 1931-1936). It is of great interest to note that these two drugs are also the cheapest of all the hypnotics in common use. *Synergism* Experimental study has shown that in some instances when two hypnotics are used together the resultant effect is greater than would result from the mere addition of their two separate effects, thus we call synergism and say that one of the drugs increases (potentiates or synergizes) the effectiveness of the other. In explanation of the phenomenon one may either postulate alteration of physico-chemical properties with resultant raising of hypnotic power, or simultaneous activity on both cortex and brain stem resulting in deeper sleep than if either site had been affected alone by a large dose of one of the drugs. There is evidence for and against both viewpoints, so that synergism remains a fascinating mystery. *Hypnotics and pain* It would be a most desirable thing if some of the hypnotics were also analgesics but unfortunately this is not so except to a limited extent in the case of chloretone. However, in some instances small doses of hypnotics synergize the pain-relieving power of the analgesics, and *per contra* small doses of

analgesics raise the sleep-inducing power of the hypnotics; both these synergisms, experimentally established, have great potentialities for clinical application.

The Chloral Group.—Though possessing the advantage of being sufficiently soluble to prescribe in solution *chloral hydrate* is objectionable in taste and very irritating to the stomach; it is a cardiac depressant only in much larger than ordinary doses (Alstead, 1930). Twenty to 30 grains (1.2–2 Gm.) usually induces sleep within thirty minutes (occasionally brief excitement precedes sleep; very rarely the drug's only action is excitatory) but does not maintain it more than a few hours. The peripheral vessels being somewhat dilated by this dose (reflecting action on the vasomotor centers), the patient should be well covered if in a cool or breezy room. Residual symptoms on the following day are quite infrequent with chloral nor is it truly habit-forming, but insomniacs tend to hold on to any crutch even after they no longer need it. The following are typical prescriptions containing 15 grains (1 Gm.) in the teaspoonful, it being permissible to allow a second dose after an hour. The first has a fruity licorice taste, the second is acid sweet; neither disguises chloral very well but this cannot be helped. As a matter of fact, I think that too pleasant hypnotics such as the barbiturate tablets now in vogue are a habit-inducing curse.

R̄ Chloral hydrate .	℥j	80 0
Fluidextract glycyrrhiza	℥ij	60 0
Syrup orange to make	℥iv	120 0
Label: 1 teaspoonful well diluted one hour before retiring		
R̄ Chloral hydrate	℥j	80 0
Syrup citric acid	℥j	80 0
Water to make	℥iv	120 0
Label Same.		

It is usually considered best to avoid the addition of alcohol to prescriptions containing chloral hydrate because of the consequent formation (especially favored by the presence of bromides) of chloral alcoholate, a substance (knock-out drops or Mickey Finn) which is much more powerfully and rapidly acting than chloral hydrate itself; this substance tends to rise to the surface so that if the bottle should not be properly shaken the patient may obtain nearly all the chloral content in one dose.

Fantus (1030) recommended the following dosage of chloral hydrate for children, to be given in starch water as a retention enema: one to two months, $1\frac{1}{2}$ to $2\frac{1}{2}$ grains (0.1–0.15 Gm.), one to two years, 8 to 12 grains (0.5–0.8 Gm.); six years, 15 grains (1 Gm.); ten to fourteen years, 25 to 30 grains (1.5–2 Gm.).

Chloral is largely reduced to trichlorethyl alcohol and excreted in the urine within eighteen hours in combination with glycuronic acid (as urochloralic acid which gives a false positive sugar reaction with Fehling's but not with Benedict's solution).

Attempts to modify chloral under the mistaken idea that ordinary therapeutic doses are dangerously depressing to the circulatory apparatus have only served to weaken its hypnotic action; a possible exception is *butyl chloral hydrate*, which is given in capsules, 5 to 20 grains (0.3–1.2 Gm.),

and is sometimes said to be of some value if the sleeplessness is caused by pain, as chloral hydrate certainly is not. Modification away from the gastric irritation has been more successful, and in *chlorbutanol* (*chlortone*) we have a product which is not only hypnotic but actually locally anesthetic, though very much milder than the cocaines and usually employed only as a dusting powder. Given internally, 5 to 20 grains (0.3-1.2 Gm) in capsules or tablets it slightly anesthetizes the gastric mucosa, therefore used as sedative in vomiting and in attempting to prevent seasickness. I think the profession would do well to use this drug more often in insomnia, since it affords chloral hypnosis without gastric irritation.

Paraldehyde is similar to and more rapid in its action than chloral but it more often produces excitement and occasionally an ordinary dose fails to be effective at all. It is a colorless liquid with odor and taste so disagreeable as very much to limit its use and also it is more irritant to the gastric mucosa than chloral hydrate. Administration sometimes causes coughing and the odor persists in the breath for a long time because the drug is partially excreted through the lungs (though principally in the urine). It is certainly less toxic than chloral in large doses but since chloral is not at all dangerous in therapeutic doses paraldehyde probably has no advantages particularly as it is prone to cause habituation despite its taste. Dose $\frac{1}{2}$ to 2 drachms (2-8 cc) on crushed ice or in highly alcoholic vehicle such as the tincture of sweet orange peel. The following is about the best that can be done, but it is none too good, perhaps diluting with sweetened iced tea instead of water as *Fantus* suggested, may be worth while.

R	Paraldehyde	3ij	60 0
	Tincture sweet orange peel to make	3iv	120 0
	Label 1 to 4 teaspoonfuls well diluted upon retiring		

Paraldehyde may also be given by rectum, diluting the dose well with water and giving as a retention enema. It is sometimes given intravenously in a dose of 1 cc to obtain its full anticonvulsant effect, as in status epilepticus (see Epilepsy).

Alcohol in the form of $\frac{1}{2}$ to 1 ounce of whisky, or a glass of wine or small quantity of beer, is a quick acting and very reliable hypnotic in those accustomed to the taking of alcohol at other than bedtime, especially aged individuals, but it will likely excite teetotalers. The effect is not long lasting because of the quick destruction of alcohol by oxidation, and of course the danger of inducing the habit of tipping must always be borne in mind.

Sulfonmethanes—*Sulfonal* dosage is 10 to 15 grains (0.6-1 Gm), best given in hot liquid, at least four hours before retiring, *trional*, in twice the dosage acts in about half the time, though with both drugs action may be much delayed. Acute poisoning need not be feared with these doses but since excretion (unchanged in the urine) is very slow neither of the drugs should be administered more than two or three times without intermission of an equal period in order to prevent cumulative poisoning with confusion, ataxia, gastro intestinal disturbances and kidney changes. Hematoporphyrin in the urine (pink or red color) is a warning sign. Because of general unreliability and the not infrequent fatal termination of poisoning cases continuance of the sulfonmethanes in our armamentarium is doubtfully justified.

Bromides—The bromides are not primarily hypnotics, however, they are often of value in aiding the patient to sleep in one of two ways (a) in small doses of 5 to 10 grains (0.3–0.6 Gm) three times daily their sedative action overcomes the hyperexcitability responsible for sleeplessness in some cases, (b) given in a single dose on retiring (10–20 grains) in combination with a reduced dose of chloral they often prolong the sleep initiated by the latter drug. Gastric irritation, bromoderma, and the other symptoms of bromism are objectionable features of bromide therapy, but one can usually detect this overaction before it has gone far (see Epilepsy).

Barbiturates—Urea, an end product of protein metabolism and a constant constituent of the body, may be converted into a powerful hypnotic by a relatively simple type of treatment in the laboratory. By varying this treatment slightly, product after product has been produced, each having hypnotic properties but each differing markedly or slightly from all others in the speed, depth and duration of its action. The following is a list of many, but by no means all, of these barbiturates. By hypnotic dosage I mean the amount likely to induce sleep in the adult when given one to two hours before retiring, sedative dosage the amount which may be given instead two, three or four times throughout the day in the attempt to accomplish the same thing.

Drug	Hypnotic dosage.		Sedative dosage
Alurate	1 to 2	grains (0.05–0.12 Gm)	$\frac{1}{2}$ grain (0.03 Gm)
Amytal	1½	3 (0.1–0.3 ")	$\frac{1}{2}$ to 1 grain (0.02–0.045 Gm)
Barbital	8	(0.5 Gm)	1½ to 2 grains (0.1–0.12 Gm)
Dial Ciba	1½ " 4½	(0.1–0.3 ")	$\frac{1}{2}$ grain (0.03 Gm)
Ipral calcium	2 " 4	(0.12–0.25 ")	
Nostal	1½ " 4½	(0.1–0.3 ")	1 to 1½ grains (0.045–0.1 Gm)
Ortal sodium	3 " 6	(0.2–0.4 ")	
Pentobarbital sodium	1½	(0.1 Gm)	
Pernoston	3	(0.2 Gm)	
Phanodorn	3 " 6	(0.2–0.4 Gm)	1½ grains (0.1 Gm)
Phenobarbital	1½ " 3	(0.1–0.2 ")	1 to 1½ grains (0.015–0.1 Gm)
Sandoptal	6 " 12	(0.4–0.8 ")	

These drugs are practically insoluble in water and are therefore usually given in tablet or capsule, preferably followed by hot fluids such as milk or beef tea. Solubility can be accomplished in such drugs as amytal, barbital, phenobarbital, etc., by introduction of sodium into the compound, but the solutions break down too rapidly to enable them to be prescribed in bottle form. When used in capsules these soluble sodium salts seem often to accentuate the period of mild excitement which rather frequently precedes barbiturate hypnotic action, thus the soluble have no advantages over the insoluble barbiturates as hypnotics.

The drugs of this group do not induce sleep as rapidly as chloral but they maintain it longer, indeed many individuals experience considerable lassitude, sometimes accompanied by headache and mild gastro intestinal symptoms, throughout the next day. Excretion is almost exclusively into the urine but varies considerably in rate and degree with the different drugs, about 85 per cent of barbital may be recovered over a period of several days, alurate, dial and phenobarbital are apparently less completely excreted, while amytal, pentobarbital and neonal seem to be entirely destroyed in the body—

however, after excessively large doses it seems that all of the barbiturates may be detected in the urine

Barbiturate ingestion occasionally causes skin eruptions and vague aches and pains about the body, and not infrequently habituation of an insidious and serious type is induced. As to choice of preparation, I repeat Grabfield's conviction, noted above, that none of the barbiturates has been proved to be superior as hypnotic to the original one, barbital.

Carbromal (Adalin) and Bromural—These drugs are neither simple inorganic bromide salts nor barbiturates, though derived from urea and having some bromine attached. Either of them in a dose of 5 grains (0.3 Gm.) three or four times daily, or 10 to 20 grains (0.6–1.2 Gm.) an hour before retiring, is of value in the type of insomnia in which sedatives rather than stronger hypnotics are indicated. Bromoderma is apparently of very rare occurrence and habit formation comparable to that with the barbiturates has not been reported. These drugs are insoluble and must be prescribed in capsules or tablets. When they maintain sleep for only a few hours it is permissible to give another 5 or 10 grains (0.3–0.6 Gm.) in the night.

Analgesic-hypnotic Mixtures—I have said above that analgesic drugs such as the salicylates and coal tar derivatives, and the hypnotics synergize each other and that this fact can be employed to advantage. But when the physician wishes to obtain either the combined advantages of analgesia and hypnosis, or wishes to obtain greater than the usual amount of hypnosis from a hypnotic drug by adding to it a small amount of an analgesic, he should write his own prescription and not merely instruct the druggist to supply so and so many of a proprietary tablet or capsule for which these advantages are claimed. Most of these preparations contain amidopyrine which it seems to me we are no longer justified in using in this loose way—see Agranulocytosis. Furthermore, it is very bad practice to do no more for the patient than advise that he buy another little tin box or glass bottle full of the tablets he knows so well. The following is the sort of prescription which I have in mind: it contains 4 grains (0.25 Gm.) of barbital and 1½ grains (0.1 Gm.) of acetanilid per capsule, so that the full dose of 2 capsules will supply the full adult dose of each of these drugs, 8 and 3 grains respectively.

R̄ Barbital	gr xlvij	30
Acetanilid	gr xvi j	11
Make 10 capsules.		
Label 1 or at most 2 capsules one hour before retiring		

Acetphenetidin (phenacetin), or acetylsalicylic acid (aspirin), either in the amount of 50 grains (so that each capsule will contain 2½ grains), might equally well have been used instead of the acetanilid. Indeed, aspirin itself, in a dose of 10 grains alone, is often astonishingly effective as a hypnotic in patients kept awake chiefly by petty annoyances and overfatigue—but it must be prescribed as acetylsalicylic acid in capsule form, aspirin purchased in tablets is not known as a hypnotic and the patient will scorn suggestion of its use for that purpose.

DELIRIUM TREMENS

This is a type of acute insanity that develops in a relatively large proportion of heavy drinkers of alcohol under any of the following circumstances (a) after a particularly heavy or prolonged bout of drinking, (b) during the first few days of an acute infectious disease, (c) following trauma, particularly fractures and injuries to the respiratory tract, (d) following the sudden withdrawal of liquor, these latter cases being of extremely rare occurrence. After one or more days of prodromal uneasiness and insomnia, the patient begins to tremble and becomes actively delirious in which state he remains without sleep for an average period of five or six days and then slowly recovers or dies, 9 per cent of the 305 patients of Rosenbaum *et al* (1941) had convulsions. The outstanding features of the delirium in typical cases are first, the fact that the patient is aware of his own personality but is disoriented as to time and the outside world, second, that he is in a state of great fear, and, third, that the hallucinations are of sight almost exclusively. The temperature remains normal in uncomplicated cases unless muscular activity is very great, the heart rate and force also correspond directly to the patient's activity except in so far as they are altered by previously existing cardiovascular disease. Delirium is usually superseded by heavy sleep of several days' duration. In severe cases the state of post-delirium stupor known as "wet brain" supervenes. Delirium gives way to semicoma and tremor to immobility, and the patient lies upon his back making "rope-climbing" movements with his hands above his head. In fatal cases the body becomes rigid and coma deepens into death. The mortality in uncomplicated cases of delirium tremens is generally reported at about 15 per cent, but in some clinics which have been specializing in the treatment of this condition it is much lower. For example, Rosenbaum *et al* (1940), at the Cincinnati General Hospital, report 594 cases with a gross mortality of 2.5 per cent and a net mortality, after omission of complicated cases, of 1.7 per cent.

THERAPY

Purgation—It is routine practice in practically all emergency or general hospitals where these cases are frequently seen to attempt the administration of a brisk cathartic at once, either a large dose of the saline or 3 grains (0.2 Gm) of calomel, followed in four to six hours by a saline.

Sedation—To produce sleep is of the utmost importance, but as a matter of fact the ordinary hypnotic drugs (see *Insomnia*) in any dosage likely to be safe are practically worthless. Paraldehyde is probably the exception, in 3 or 4-drachm (12 or 16 cc) doses several times daily it is at least well borne if not always effective (see *Index* for other methods of administering this drug). Sperber (1936) reported excellent results with the intravenous administration of sodium evipal, 2 to 3 cc of a 10 per cent solution. The patients, who had to be manhandled in order to get the drug into them, went off to sleep at once, roused briefly after two to four hours, and then sank again into sleep for another eighteen to twenty-four hours, there was no sign of delirium upon final awakening.

Morphine is nowadays considered to be dangerous to use because of its alleged ability to increase intracranial pressure. Nor is there any longer any doubt that alcohol is contraindicated. Lambert wrote that apomorphine

hydrochloride, 1/10 grain (0.006 Gm.), combined with strychnine sulfate, 1/30 grain (0.002 Gm.), often has excellent sedative qualities. Physical restraint as a method of treatment is no longer popular and is, indeed, looked upon by many observers as needlessly combating the sufferer.

Cerebral Dehydration—A good many years ago spinal drainage and the use of hypertonic solutions intravenously were separately reported upon. Cline and Coleman (1936) combined these methods and were very favorably impressed with their results during a two year period in an active psychiatric institute. Their routine treatment consisted of the following: (a) spinal drainage of from 50 to 75 cc. of fluid, (b) intravenous administration of 50 to 100 cc. of 50 per cent dextrose solution, (c) magnesium sulfate by mouth, 1 to 2 ounces (30–60 cc.) of saturated solution, (d) limitation of fluid intake to 1000 cc. for twenty four hours. Piker and Cohn (1937) also highly recommend spinal drainage and state that in approximately 1500 cases of acute alcoholism and delirium tremens they have never seen it do any harm, but they recommend that the fluid be allowed to escape slowly, and more recently, Rosenbaum (1941), of their group, finding that the spinal fluid pressure was normal in 70 per cent of 211 cases, indicates that while the measure is valuable it should be looked upon more as an aid to differential diagnosis than to therapy. The matter of fluid limitation has also come in for criticism recently. Piker (1938), of the Cincinnati group, studied 150 patients, half restricted to 1000 cc. and half given 3000 to 4000 cc. of fluid, his conclusion was that the advantage lay neither way, in fact this group of workers now seem to feel that the most important elements in therapy are hospitalization, spinal drainage, the use of paraldehyde, and more attention to psychotherapy than has previously been the custom. However, other groups such as Bowman *et al.* (1930) of Bellevue Hospital favor the forcing of fluids unless there are contraindications.

Sodium Chloride, Carbohydrates, Vitamins—It has been empirically observed that some patients are helped by the administration of both carbohydrates and sodium chloride in rather large amounts, some men therefore incorporate these measures in their plan of attack. Others have found thiamine hydrochloride (vitamin B₁) and nicotinic acid of value, but Wortis (1940), reviewing the subject, finds the evidence in favor of such vitamin therapy very meager.

Supportive Therapy—The whole gamut of these drugs is usually run, but it is not a matter of record how much is accomplished thereby. Piker and Cohn, in 1937, very much favored beginning digitalis therapy as soon as the diagnosis is made, and when digitalization is reached in thirty six to forty-eight hours continuing with maintenance dosage until recovery is complete, their belief at least at that time was that to withhold digitalis in these patients until heart failure has set in is to court disaster.

A General Plan of Treatment.—From all of the above it will be seen that there is a bit of confusion and contradiction in the therapy of delirium tremens today. Therefore it may possibly be helpful to set down here a clear outline of the procedures as followed at Bellevue (Wortis, 1940).

1. Withdraw alcohol abruptly.

2. Give sedative medication judiciously, paraldehyde being preferred, and morphine condemned.

3. Omit restraints unless absolutely necessary.

- 4 Give carbohydrate in large quantities
- 5 Administer sodium chloride in an attempt both to combat dehydration and to restore the normal acid base equilibrium of the body
- 6 Provide a high-calorie, high vitamin diet
- 7 Force fluids
- 8 Do lumbar punctures for diagnostic purposes only
- 9 *Treat complicating or precipitating factors with specific therapy*
- 10 Give individual psychotherapy according to the needs of the patient

SEASICKNESS

There are some individuals who suffer from loss of appetite and low grade nausea, but not actual vomiting throughout the first few days of a voyage and then recover their normal feeling of well being, others there are who experience only an excruciating headache without the least gastrointestinal symptoms, but the symptoms in the most frequent type of the malady consist in discomfort in the epigastrium, anorexia, salivation, headache, dizziness, weakness, cold perspiration, greenish pallor, great dejection and bouts of vomiting with or without nausea. Most cases terminate spontaneously after a few days at sea, but there are individuals who suffer continuously throughout an entire voyage. Even professional seafaring men are occasionally made slightly ill when the ship begins to pitch or roll in an unusual fashion, particularly if they walk to a part of the vessel which they are not in the habit of visiting.

Though I have placed seasickness in this book among the disturbances of the nervous system, the truth is that despite the respectable antiquity of the malady we are still without an entirely satisfactory explanation of its etiology. Each of the following has at some time been urged as the sole cause, but it is more probable that all of them operate to some extent in varying proportions in each case. (a) The labyrinthine theory suggests that the upset is caused by overstimulation of the equilibratory organs in the internal ear, with resultant overflow of stimuli from these to other centers, such as the vagus. (b) The theory that confusion results from the multiplicity of ~~anterior~~ stimuli coming along those sensory nerves that ordinarily have to do with the adjustment of our bodies in space. (c) The theory that there is excessive discharge along either parasympathetic or sympathetic pathways depending upon whether the individual is "vagotonic" or "sympatheticotonic." (d) The theory that eyestrain caused by the glare of the sea and sky, and the unusual fixation upon moving objects reflexly causes the symptoms. (e) The theory that the wide excursions made by the freely movable organs of the abdominal cavity unduly irritate the vagus nerve. (f) The theory that autosuggestion is causative. (g) The theory that the malady is an acidosis.

THERAPY

Postural Treatment—Unless the psychic element is uppermost, the patient probably profits most by lying in the prone position with the head very little, if at all, raised. The nearer the center of the ship he stays the

better Sudden movements should be avoided, such as bending forward or getting up rapidly, or hurriedly ascending or descending the companionway.

Value of Fresh Air—The patient should recline on deck, if possible, however, many patients are embarrassed by their illness in the presence of others, and can relax freely only in the privacy of their cabins, in which cases all facilities for maintaining the circulation of the air in the room must be utilized.

Prevention of Eyestrain—The seasick individual should be facing the deckhouse and not the sea and should avoid using the eyes as much as possible, reading only for brief periods and keeping the eyes closed at other times. Some persons immerse themselves in a darkened cabin as soon as they board ship and leave it only when the port of destination has been reached. Perhaps a few thus avoid illness, but the fact should not be overlooked that blind persons also suffer from seasickness.

Plugging of the Ears—The simple procedure of plugging the ears with cotton is said to relieve the symptoms in some instances, what is put on the cotton is of course of no importance—indeed, I think the sole effect is psychic.

Abdominal Binder—The use of a tight binder across the lower abdomen has many staunch supporters among experienced travelers, most physicians believe that only those who suffer from visceroptosis are thus relieved. However, during my own brief experience as a ship surgeon one of my fellow officers repeatedly demonstrated to me that he became quite ill whenever he removed his binder in a heavy sea. This man was apparently not visceroptotic, though of course x ray studies were not made, nor do I believe that he was under any psychic thrall to his belt for he had followed the sea for many years and had only recently discovered that he could pass unscathed through storms in this way.

Diet—On this head Oriel (1927) writes: One finds that if passengers can be persuaded to eat plenty of fruit and carbohydrates and to avoid fats that they are never violently sick. The common error is to avoid food, which, of course, leads to early exhaustion of the glycogen reserve. Acidosis is the inevitable sequel. Once this train of events is in progress other factors, such as inability to take food and constant vomiting, tend to make the acidosis more severe. Seasick persons should eat, no matter if they lose one meal after another for vomiting something is easier than the endless retching of an empty stomach. Swallowing small chunks of ice or sipping cold ginger ale or champagne, is often a helpful measure in dispelling nausea.

Certainly the excessive smoking and drinking in which many individuals indulge while at sea cannot but aggravate the bout of illness when heavy weather comes.

The following carminative mixture will hasten the passage of the stomach contents into the duodenum, and may prevent the onset of the complete syndrome in an individual who is only slightly nauseated.

R	Tincture of capsicum	℥ss	2 0
	Spirits of pepper mint	℥ij	8 0
	Tincture of ginger	℥ij	60 0
	Alcohol to make	℥iv	120 0

Label: 1 teaspoonful well diluted after meals may be repeated if desired.

Dextrose—The suggestion of Jones (1925), somewhat substantiated by the findings of Oriel (1927), that seasickness is an acidosis entirely curable by dextrose, has been questioned by both Marrack (1931) and Maitland (1932), on the basis of much experience. It is not doubted by these latter authors, however, that dextrose given intravenously or rectally, or by mouth if it can be retained, is helpful in some instances.

Cathartics—The normal individual should be warned that he is liable to become somewhat constipated during the voyage and will do well to employ a simple cathartic on any day that he has not gone to stool. I think the drastic catharsis induced by many voyagers before they board ship is unnecessary.

Belladonna, Atropine (or Scopolamine), Strychnine and Benzedrine—Girard many years ago advocated the use of atropine sulfate, $\frac{1}{100}$ grain (0.0005 Gm) combined with strychnine sulfate, $\frac{1}{80}$ grain (0.001 Gm), subcutaneously, at the beginning of a voyage, during rough weather, or on the advent of a storm, this dose to be repeated twice, at hourly intervals, or until incipient dryness of the throat and disturbance of vision indicate its discontinuance. Lundy (1938) quoted the surgeon of the Italian liner *Rex* as saying that 1/100 grain (0.001 Gm) of atropine alone and given intravenously will almost instantaneously bring relief. I believe that the attempts to prove the rationale of the atropine-strychnine combination based upon the pharmacologic actions of its components, have not been fortunate, but it is certainly a clinical fact that the mixture does often relieve seasickness. Some men prefer scopolamine hydrobromide (hyoscine) to atropine. Desnoes gave 1/400 grain (0.00016 Gm) every hour until relief was obtained or signs of overaction appeared, adding strychnine when depression seemed to indicate. The most recent writer of considerable experience to testify to the value of this general type of therapy is Hill (1937), of the *Aquitania*, he has also used benzedrine sulfate in 10 to 20 mg dosage to good effect in 70 of 100 patients, though in only 39 was the improvement unequivocal.

Sedatives—The whole gamut is of course run, but many men prefer chlorbutanol (chlorotone) in doses of 5 to 10 grains (0.3-0.6 Gm) in tablets or capsules, to all other drugs, it may be given three times daily if it is desired to induce sleep as well as control the vomiting. In my own brief experience I several times saw chlorotone in 5 grain doses succeed when other sedatives had failed.

Morphine and Rectal Feeding in Excessive Vomiting—Desnoes described his handling of these cases as follows: "Cases of excessive vomiting that tax our efforts at control are occasionally encountered. After the usual remedies are tried, including the mustard plaster applied to the epigastrium, from $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008-0.015 Gm) of morphine sulphate, administered hypodermically, combined with from $\frac{1}{100}$ to $\frac{1}{80}$ grain (0.0003-0.0004 Gm) of atropine sulphate, is the court of last resort. Provision must be made for the curious fact that the drug most potent in checking vomiting is followed by vomiting as a common after-effect. After the patient awakes from the sleep induced by the drug, he should be directed not to raise his head from the bed for several hours. Iced brandy, champagne or strong coffee may be given through a drinking tube, but if nausea reasserts itself it is best to continue the administration of morphine, combined with atropine, in progressively descending dosage, using perhaps every four hours half the previous

dose If neither food nor water can be retained in the stomach for twelve hours or so, no time should be lost in resorting to rectal alimentation The only substances of food value that can be absorbed from the lower intestine are amino acids, simple sugars and alcohol The old method of trying to maintain nutrition by the introduction of ordinary foodstuffs through the rectum has been shown to be efficacious Skimmed and pancreatinized milk may be used, or the clyisma suggested by Smithies alcohol, 50 per cent, 1 ounce (30 cc), glucose, 1 ounce (30 cc), physiologic sodium chloride solution, sufficient to make 8 ounces (240 cc) Karo corn syrup is a concentrated solution of practically pure glucose and is easily obtainable This injection should be administered at body temperature by the drop method, with the patient on his back and the hips elevated, it should be repeated two or three times during the day A bulk of 10 ounces (300 cc) should not be exceeded Needless to say, feeding by mouth should be resumed as soon as possible, commencing with such easily digestible articles as milk, bouillon tea, ice cream and arrowroot crackers

Oxygen —In a general paper on the uses of oxygen in 100 per cent concentration Boothby *et al* (1939) list seasickness as a malady which is always benefited if not entirely controlled, but I have unfortunately not seen the account of the studies upon which this statement was based

Psychotherapy —Many individuals, especially first-trippers, agitate themselves into a very nervous state before they board ship and are almost certain to develop seasickness as soon as the ground swell is felt In these cases it is perhaps advisable to use small non narcotic doses of the sedatives for several days before the voyage is begun, advising the ship surgeon when possible what has been done in order that he may be guided in his medication during the first few days at sea, indeed, the carrying of a note to this officer, with a request for what is looked upon as "special care," often has a profoundly helpful effect upon nervous individuals who dread the ordeal of a bout of seasickness alone on a large ship, upon the reaction of the plagued surgeon let us draw the charitable curtain!

Helpful admonitions regarding conduct during the voyage are the following (a) divert yourself in the company of others as much as possible, but do not plunge too strenuously into unwonted exercise, (b) look shipward instead of seaward for the first few days, but do not "strain" yourself to do this else it will only serve as a reminder of the ever lurking illness, (c) avoid the sight of sick individuals as much as possible, (d) go in jauntily to meals as soon as they are announced for procrastination often spells disaster at this juncture, (e) if on a small ship, keep to windward of the deckhouse in order to avoid the odor of cooking food

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GERIATRICS

GERIATRICS

(The Care of the Aged)

In recent times there has come to be a certain amount of fuss and bother about the necessary and impending reorientation of medical thought toward the diseases of the aged who are steadily increasing in numerical proportion in our population. In some quarters I know that young men are being urged to specialize in geriatrics. For my own part, however, I am unable to become quite as disturbed by the new prospects admittedly perhaps I should be. My "objections," if one wishes to call them that, are two, which will be developed below.

In the first place the analogy between pediatrics, the medical science at the one end, and geriatrics the medical science at the other end of the span of life, is basically unsound. The reasons for this basic unsoundness have been expressed by Kniskern (1940) so much more ably than I could do it that I shall merely summarize his reasoning here. His position is that the child has no objection to being a child and knows that he will soon get over it, whereas the oldster has been dreading old age all his life and knows that it will not only continue but get worse. Furthermore, the aging individual firmly opposes admitting to himself or to anyone else that he is growing old, and he (perhaps even more positively she!) will certainly not willingly walk into the office of a physician known to treat only the diseases of the aged. So it seems to me that the young men who have chosen geriatrics as their specialty might do well to prepare for a practice confined almost exclusively to institutions and clinics since if any form of private practice survives in this country they are not likely to have many fee paying patients enter their own offices.

In the second place a little thought regarding the "diseases of the aged," will reveal that there are very few entities which can be placed categorically in this class. Barker's (1939) 240 aged patients presented with the following complaints in the vast majority of instances: disturbances of the nervous system, disturbances of the digestive system, disturbances of the circulatory system, and disturbances of the locomotor apparatus. Barker furthermore says that about 50 per cent of deaths among the aged are from circulatory disturbances, about 12.5 per cent from respiratory disturbances, about 12.5 per cent from cancer, about 8.5 per cent from diseases of the kidneys, especially chronic Bright's disease, about 6.5 per cent from diseases of the gastrointestinal tract other than cancer, and the remaining 10 per cent from diseases of all other organ systems and from accidental injuries. Of course one needs to particularize a bit among these categories but there is certainly nothing very distinctive in this list. Therefore in what follows I shall merely have a little to say with regard to these entities and such other matters bearing upon geriatrics as seem to come within the province of this book, warning the reader in passing that not even the merest trickle from the fountain of youth will splash him as he turns the pages.

Circulatory Disturbances—There is a chapter upon this subject elsewhere in the book, in the course of which such considerations as bear upon the age of the patient are given what I hope is due consideration. There is really nothing else to add at this place.

Respiratory Disturbances—This subject too has a chapter of its own, and such of the entities as are of an infectious nature are discussed separately under their own titles in the chapter on infectious diseases. One might remark that tuberculosis causes death among the very aged only occasionally and that pneumonia, once the "old man's friend," is leaning away from him now that the sulfonamides have come upon the scene. But pulmonary emphysema, which may lead to circulatory breakdown through overburdening of the right side of the heart, remains a serious problem.

Nephritis—This subject, in both its acute and chronic phases, is discussed elsewhere in the book in a chapter of its own.

Gastro-intestinal Disturbances—These ailments too have their own chapter. Perhaps it is pertinent to remark that it is the consensus that peptic ulcer is rare in the aged but that, when it is present, it is apt to be very severe, and, if there is hemorrhage the bleeding is likely to continue for a long time because of the relative rigidity of the vessel walls, and perforation is of more frequent occurrence than among younger individuals. A note worth adding here is that the accelerated pulse indicative of continued bleeding may not occur in the aged. Meyer (1940) points out that if the activity of the ulcer is dependent on the digestive action of free hydrochloric acid and pepsin one would expect fewer perforations in the aged because of the diminution in the acid and enzyme, still, relatively more perforations occur. Dyspepsia in the aged, a less serious seeming matter, should nevertheless be investigated, for often dyspeptic symptoms are merely the signpost pointing toward the heart as the real cause of the trouble. Ivy (1939) says there is no reason to believe that constipation is more common in the aged than in younger individuals, remembering that constipation as a complaint may be present in a patient when true constipation is not. Nevertheless, rectal constipation often leading to fecal impaction is seen with greatest relative frequency in institutions for the aged according to most observers. If soap-suds or milk and molasses enemas will not relieve the impaction manual removal must be resorted to. Diverticulosis is merely a nonsymptomatic radiologic diagnosis, but diverticulitis, which is an inflammatory reaction in a diverticulum, gives rise to symptoms and occurs usually in early old age. This is usually considered a surgical problem, but Meyer (1940) says that in his experience the majority of these lesions have become localized and resolved without extension or complications.

Finally, what to do with the aged individual whose symptoms point toward the need for a thorough gastro-intestinal study? Meyer (1941) has well pointed out that there is a deplorable tendency to employ merely simple symptomatic treatment in such individuals, and he makes a plea for full employment of all laboratory diagnostic aids. He is doubtless right and justified, but let us, please, be gentle and bring these oldsters gradually up to the harnum and x ray bout which would be a dreadful ordeal even for some of us prime and cocky youngsters.

Cancer.—Despite the contrary opinion of some kind friends of my book it still seems to me that this great subject, being still in essence surgical, is

not one which I should include. However, a few notes regarding intractable pain seem in order.

New Methods of Employing Opiates—The great drawback to the opiates is of course the fear of causing addiction, not that we are desirous of avoiding this for its own sake since these patients are but waiting to die anyway, but addiction brings with it symptoms of its own and often so alters the patient's personality as to make the final ordeal additionally difficult for the family, furthermore, addiction implies diminishing analgesic returns per gram of morphine, dilaudid or pantopon, and the cost of the necessarily large amounts of these drugs is often very great. Recently two measures have been described which merit mention here even though a thorough trial of them has not been made as yet. One is the combination by Slaughter *et al* (1940) of morphine and prostigmin methylsulfate, they give a reduced dose of morphine in 1 cc of 1:2000 solution of the prostigmin salt and report an apparent potentiation of the action of the morphine. The other is the employment of small morphine dosage by continuous intravenous drip, as described by Neuhof (1941). Morphine sulfate, in the quantity of $\frac{1}{2}$ grain (0.04 Gm), is added to 1000 cc of physiologic saline solution and 100 cc of this solution (containing $\frac{1}{20}$ grain (0.004 Gm) of morphine) is given intravenously per hour continuously. This method was described for postoperative use, but I think that it might be made to fit into some desperate terminal cancer pictures since Neuhof ascribes to it remarkable analgesic action with almost complete absence of the other and objectionable morphine effects of course for one already addicted the dosage would doubtless have to be raised considerably.

Cobra Venom—This agent is by no means regularly effective but is worth trying on the off chance that it will give relief. Unlike the opiates it must be given over a considerable period before relief may be expected, thereafter the doses are given less often in order to maintain the effect. Greenhill's (1941) routine is typical: begin with $2\frac{1}{2}$ mouse units, raise the next day to 5 or 10 units, and continue this dosage daily for about a week, thereafter, if analgesia has been obtained the patient may be kept comfortable with two or three injections weekly, but if success has not been obtained by the initial seven days of injection it is useless to persevere. The material is not expensive, there is little local and I believe no systemic reaction, injections are given intramuscularly.

Intraspinal Alcohol Injection—It now seems to be established that in the majority of instances intraspinal alcohol injections give relief which may last several months. Of course this is a radical procedure since the spinal cord may be injured but the risk may certainly be taken in such cases as are under present consideration. In the accompanying chart, published by the kindness of Dr. Elias Lincoln Stern, of New York City, the sites for injection are shown. In what follows I present Greenhill's technic for injection in cases of pelvic malignancy to serve as model for this procedure.

"No preliminary medication is given because we wish to observe the immediate effects of the injection. Most patients with advanced carcinoma of the pelvic organs have much more pain on one side than on the other. The patient is placed on the side opposite to that where most of the pain is present. A pillow or pad is placed under the pelvis and side to elevate the sacral and lumbar portions of the spine, the back is arched as much as pos-

sible the body is turned somewhat ventrally, and the head is lowered slightly. By placing the patient in this attitude we raise the sacrolumbar region of the spine to the highest level and at the same time make the posterior or sensory nerve roots lie horizontally. The anterior or motor nerve roots come to lie in a plane which is usually out of reach of the alcohol. Even if the motor nerves are not removed from the field of the alcohol as occurs in the cauda equina they are not often affected because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

'Someone should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. Injection is made in the second, third or (usually) fourth lumbar interspace. An ordinary lumbar puncture needle with a stylet is used. The needle is inserted into the desired interspace just as for an ordinary lumbar puncture and novocain is injected into the skin before inserting the needle. After the needle is in the subarachnoid space as evidenced by the flow of spinal fluid 0.75 cc. of absolute or 95 per cent alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe in order to make sure that not more than 0.75 cc. of the solution is injected. Furthermore the alcohol must be injected very slowly drop by drop allowing about two minutes for the injection of the 0.75 cc. The alcohol rises immediately to surround the posterior roots because the specific gravity of alcohol is about 0.800 whereas that of the spinal fluid is 1.007 to 1.011. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol in fact this is exactly what is not wanted. After the injection is made the needle is withdrawn and the puncture hole is covered with sterile gauze and adhesive.

'Before the injection is completed the patient will complain that the upper leg feels numb or hot and that the leg cannot be moved. The numbness is almost routinely experienced after the injection but disappears spontaneously after a few hours or few days in most instances. In spite of what the patient says concerning inability to move the leg when he is requested to move it he will meet no difficulty. At the time the patient informs us of the numbness he also often tells us either voluntarily or in answer to our query, that the pain has disappeared. The longer the patient is permitted to lie on the side the better the results. Hence the patient should be kept on the side for two hours after the injection after which period he is permitted to get up and walk around. Sometimes a patient finds difficulty in getting up from a chair because his leg is asleep. In other instances the leg feels heavy and the patient experiences some trouble in walking up steps because the knee flexes readily. These sensations usually wear off in a few hours although in some patients they last a number of weeks.

Nearly all of the patients who are ambulatory may be permitted to go home within three hours after the injection. No ill effects will be observed from this procedure. It is perhaps best however to keep a patient in a hospital for twenty four hours after an injection. I should like to emphasize that the intraspinal injection of alcohol may easily be carried out in a patient's home. This is important to remember because many individuals with cancer are bedridden at home and there is no need to subject them to the inconveniences and expense of transportation to a physician's office or a hospital.

'If the patient has pain on both sides an injection is made a week later

OUTLINE FOR REGIONAL ALCOHOLIC PAIN BLOCKING*

Organ involved		Type of block	Site of injection.
Head		Trigeminal block	I II III divisions (a) Terminal nerves (b) Subganglionic block (c) Gasserian ganglion block
		Stellate ganglion sympathetic block	(a) Paravertebral between first and second ribs (b) Subarachnoid T 1-2 Especially important in connection with trigeminal pain or neuralgia
Neck		Cervical plexus block	Paravertebral
Upper extremity		Subarachnoid block	T 2-3 Exceptional T 1-2
Chest	Larynx Trachea Bronchi Lungs Heart†	Subarachnoid block	T 3-4
	Aorta† Esophagus†		Upper part T 3-4 Lower part T 8-9
	Pleura		Entire T 6-7 or T 7-8 Upper part T 3-4 Lower part T 8-9
Abdomen	Aorta† Spleen	Subarachnoid block	T 5-6
	Stomach† Liver† Pancreas† Small intestine†		T 6-7 or T 7-8
	Colon†		T 11-12 or T 12-L 1 Ascending and transverse colon T 4-5
	Kidney suprarenal gland		T 11-12
Pelvis	Ovaries Testicles Uterus† Tubes Ureters Seminal vesicles Prostate† Urethra† Bladder†	Subarachnoid block	T 12-L 1 and L 4-5
	Rectum—anus†		L 4-5
Lower extremity		Subarachnoid block	T 11-12 (Sympathetic) and L 1-2 (somatic)

* In blocking the long viscera, aorta small and large intestines or in special cases it may be necessary to repeat the block one or several segments higher or lower than the levels given above. This outline applies only to the adult body.

† Lesions affecting these organs usually involve the sympathetic nerves of both sides. Bilateral (right and left) injections should be given in these cases.

with the patient lying on the opposite side. The same amount of alcohol is injected."

Other Measures—Sympathectomy or cordotomy are sometimes resorted to in selected cases, of course these are operations requiring very special training. Latterly refrigeration and "hiheroation (crymotherapy)" have been employed experimentally but these methods have certainly not reached the stage of general practical application nor would it seem that they are likely to do so.

Diabetes Mellitus—Here is a disease which affects the aging more than the truly aged, it has a chapter of its own elsewhere in the book.

Fractures—The breaking of a bone, which used to be viewed as an unmitigated calamity for an oldster, is nowadays not nearly so serious a matter, thanks to the orthopedic surgeons who are insisting upon active movements immediately after recovery from the anesthetic.

Prostatism—Here is certainly a distinctive disease of the aged, the hypertrophied prostate a urological matter which of course has no place in this book. Spinal anesthesia, the transurethral resection technic, and the sulfonamides are a triad to which the world's old men should erect a monument. Clark (1939) has performed prostatectomy under general anesthesia in a remarkable negro man aged 110 years, who came into the clinic one year later to report himself very well!

Other Surgical Matters—In this field, which is likewise outside the province of this book great advances have also been made so that nowadays even elective surgery is performed in individuals of quite advanced years. Some factors which have contributed to this happy state of affairs in recent times are (a) recognition of the necessity for painstaking preoperative measures to prevent postoperative complications by eliminating them "at the source" where possible, (b) the gradual passage of anesthesia into trained hands coupled with the introduction of less toxic general anesthetics and the increasing employment of spinal anesthesia, (c) postoperative care designed to oppose atelectasis by ensuring complete ventilation of the lungs i.e., the inhalation of carbon dioxide at intervals, (d) the attempt to prevent pulmonary embolism through centripetal massage of the legs and active and passive movements of the limbs in order to promote venous return as much as possible, (e) recognition of the necessity to get these old people up out of bed and moving around on their own power as soon as possible in order not only to prevent thrombosis but also the type of cardiac failure which may result from loss of cardiac reserve while lying in bed (and old people become terribly depressed in bed too, feeling that now at last their time has come), (f) the recognition that fluids should be "pushed" only very slowly if at all in these patients and that any measures—venoclysis, hypodermoclysis or proctoclysis—which keep the patient long on his back are likely to be extremely dangerous, (g) the use of the sulfonamides.

Eyes and Ears—Cataract and glaucoma, and degenerative and vascular changes of the eyes are predominantly diseases of the aging and the aged, as is also impairment of hearing. But it cannot be expected that a discussion of such things will be found in a book of this nature.

Diet and Vitamins—It has been known for some time that hydrochloric acid and pepsin secretion decrease with advancing years and now recently the information has been added that salivary and pancreatic (except amylase)

secretions also diminish. But Meyer and Necheles (1949), who have carefully studied these matters find that the secretory mechanisms are capable of response under adequate stimulation and that the quantitative alterations apparently do not affect intestinal digestion. They conclude that restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein or fat do not appear warranted. In other words, old age in itself is no reason for dietary alterations. Experience has shown in fact that with few exceptions old people select both the quantity and quality of food which satisfies their needs and taste. Loss of appetite, however, is a matter which often requires serious attention. It may be due to loss of teeth or poorly fitting false teeth which necessitate a change to a soft unattractive diet and ultimately lead to a loss of interest in food. Then, too, there are changes in the taste buds and diminution in the senses of sight and smell. To stimulate such lagging appetites bitters have long been used before meals, such as a teaspoonful in water of the compound tincture of either cinchona or cardamom, or a little dry wine to be taken with the principal meal of the day. Latterly, thiamine hydrochloride (vitamin B₁) has begun to be used with apparently excellent results—dosage is usually a 3 mg. tablet after meals once, twice or thrice daily as indicated by results. There are undoubtedly cases in which the prohibition of tobacco smoking would be helpful in stimulating the appetite, but the advisability of attempting such a radical deprivation must be carefully weighed in each individual case. In this group of elderly individuals with jaded appetites, and especially in those with dietary restrictions self or otherwise imposed, true vitamin deficiencies can now and then be found.

Disturbances of Locomotion—In speaking of the infirmity of old age we probably most frequently have in mind the weakness in the legs and difficulty in locomotion which so often accompany the state. It seems that stiffening of the joints results to a considerable extent from failure in lubrication as well as from aging of the nerves and muscles. Some of the cases are of course due to osteoarthritis fibrositis or gouty arthritis—subjects which have a section of their own in the book. And then there is the group of cases which lies entirely within the realm of the neurologists, the relatively rare cases of senile paraplegia and senile cerebellar and amyostatic syndromes. I believe there is nothing to do for these latter save make the diagnosis.

Neuropsychiatric Disturbances—Many old people develop tremor, particularly of the head, which is very annoying and embarrassing to them but about the best one can do in these cases is to give assurance that the shaking is not a forerunner of paralysis agitata and is not as noticeable anyway as the patient thinks it is. True paralysis agitata with its characteristic flexed position of the extremities bent-over posture, shuffling gait, and general rigidity combined with tremor is a truly unfortunate affliction for which practically nothing can be done. The drugs used to combat postencephalic Parkinsonism are of course tried (see Encephalitis), but their effectiveness is usually slight here. If every effort is made to remain active both physically and mentally it is sometimes surprising to observe the small extent to which this degenerative process limits the individual's participation in daily affairs. The tendency to become dependent upon another, usually the husband or wife, for the performance of most acts must be rigorously opposed from the beginning.

The aged often do not sleep well at night, being not so much disturbed in their sleep as simply sleepless. Sometimes daytime napping makes up some of the loss, indeed this is almost universally the case. However, insomnia in the aged, though often the subject of bitter complaint, is rarely a matter of serious concern for it seems that the aged body actually requires to spend a smaller proportion of the twenty-four hours in slumber than does that of the person in early or middle life. The happiest solution is for the aged individual to find something to do—read, play solitaire, etc.—while the younger members of the family are getting their needed sleep. Certainly one should be very chary of employing hypnotics in these oldsters for they sometimes react in a very excited manner to these drugs, the bromides and barbiturates seem to be the worst offenders in this respect. Alcohol is the safest nightcap if one is to be employed at all.

The mental deteriorations pacing the advancing years are too well known to require more than mere listing. disinclination to accept anything new in either ideas, foods or habits, failing memory, especially for recent events, excessive worry about the financial future, suspicious tendencies, and an increasing sensitiveness, so that we say "grandma is so easily hurt" nowa days. The summed expression of these things depends entirely upon the individual and the family environment—if luck is good the oldster may become the dearest and most charmingly influential member of the household, but luck is not always good.

The true senile psychoses must be left to the psychiatrists, it seems to me. They have done a deal of describing and classifying of them, and certainly should be called in before the awful step is taken of committing any patient. Some alleged senile psychoses have turned out to be only toxic states which have cleared up under proper eliminative and supportive therapy, Robinson (1941) has taken the lead in advocating 10 per cent dextrose intravenously in selected cases and even shock therapy in some instances, work which certainly bears watching.

DISEASES OF THE SKIN

DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA

Impetigo is an acute contagious disease of the skin with a predilection for the face. It is sometimes spread among adult males by barber shop infection, and an occasional case is seen in an adult female, but the great majority of patients are children within the school years. There are a number of varieties of this malady, but the most common one is characterized by a sudden crop of localized erythematous areas, upon which rapidly appear thin walled vesicles and bullae, these lesions soon become pustular and then dry up quite rapidly, leaving thin, honey-colored loosely attached crusts that drop off without scar formation, though the hyperemia fades out of the affected areas rather slowly. There is usually no itching. Both staphylococci and streptococci have been obtained from the lesions.

THERAPY

Ammoniated Mercury—The most usual treatment of this condition is to cleanse the parts thoroughly with soap and water, breaking all bullae with gauze or a sterile toothpick, and then apply an ointment of 1 to 2 per cent ammoniated mercury, sometimes increasing to as much as 10 per cent. This used to suffice to cure most cases in one to three weeks, but of course to keep a grease applied to the face during working hours is objectionable to adults. In children this objection does not apply for they should be kept out of school in any case. I say 'used to' advisedly, for it seems to be the opinion of numerous dermatologists that ammoniated mercury is not today as effective in impetigo as it was some years ago.

Colloidal Calomel—At the Cook County Hospital, Cornbleet *et al* (1939) have been using an ointment containing "colloidal" calomel which they say clears up the cases in one third to one-half the time required by ammoniated mercury.

Gentian Violet—This agent, usually painted on the lesions in 1 to 2 per cent aqueous solution, has become very popular in recent years, but I have seen no report of its extensive employment in direct comparison with the other agents—would it not, in fact, be worth the while of one of the large dermatologic clinics to make a controlled and comparative study of all the preparations which are currently being applied in the treatment of this condition?

Quinoline Compounds—In a small number of cases, Seldowitz (1940) has used a rubber base containing 8 hydroxyquinoline with very satisfactory results, the crusts disappearing in an average time of three days and the skin regaining its normal appearance in eight days. The lesions are covered with a thin layer of gauze and the rubber is applied over the gauze, the dressings being held in place with adhesive plaster and changed every two to four days. Carpenter (1939) earlier reported the use of an ointment containing 0.25 per cent chlorhydroxyquinoline and 5 per cent benzyl peroxide in equal parts of hydrous wool fat and petrolatum, results seemed to be at least equivalent to those obtained in his control ammoniated mercury cases.

Silver Nitrate—Morrow has advocated the use of silver nitrate applied with a swab in 20 per cent solution after cleansing the lesions and opening the bullae. He and others have found this treatment very efficacious, but open to two objections: first, that there is some pain on application of the solution, and, second, that a black unsightly crust appears quickly and remains for three or four days. Sutton uses only a 10 per cent solution. The organic silver preparations (argyrol, etc.) have been found ineffective. After the application of the silver nitrate solution, Highman applied an ointment of ammoniated mercury or 10 per cent balsam of Peru.

Dusting Powder—Morrow writes: "It is advisable to apply a dusting powder, preferably one containing ammoniated mercury in the strength of from 6 to 10 per cent, and a boric acid powder up to from 15 to 20 per cent. When impetigo is on the uncovered part, even without the silver, the powder form of treatment should be selected in preference to a grease. Customarily I have applied such a powder after swabbing with silver solution, and order its use by the patient several times daily."

R	Ammoniated mercury	℥iss	6 0
	Zinc oxide	℥v	20 0
	Talcum to make	℥ij	60 0
	Make a dusting powder		
	Label: Apply as directed		
R	Boric acid	℥iij	12 0
	Zinc oxide	℥v	20 0
	Talcum to make	℥ij	60 0
	Make a dusting powder		
	Label: Apply as directed		

Salicylic Acid—Lain states that after the secretions and scabs are removed by cleansing methods, he applies a 50 per cent alcoholic solution of salicylic acid in cases in which it is deemed that the patient can stand the treatment. This does not stain unless repeated and, in his hands, has been of especial value in preventing spreading.

Iodine.—One per cent iodine in alcohol is sometimes used to paint the lesions; the stain does not persist so long as that of the silver nitrate.

Metaphen in Collodion—Hollander and Hecht (1934) wash with soap and water and dry the skin around the infected area and then paint the lesion with several layers of metaphen 1:500 in collodion. In 24 hours they take off the removable layers and reapply the mixture, repeating the procedure on the third day; on the fourth day all layers are removed, including the underlying encrustation—if the surface is still moist reapplication is made, if dry 2 per cent ammoniated mercury ointment is used.

Copper and Zinc Sulfate—Brownson writes: "In my opinion there is little need for treating the ordinary cases of impetigo so actively. I have used a modified form of *l'eau d'Alibour*, the favorite treatment of Sabraud. A modification of his remedy, which does very well, is made up of 1½ grains (0.1 Gm) of copper sulfate and 3 grains (0.2 Gm) zinc sulfate to the ounce (30 cc) of camphor water. I often start by removing the crusts by a boric acid starch poultice, and when removed, sop on the solution named several times a day, and its results are usually prompt. It is cleanly, and I can hardly see how it could be improved on. I think the results are fully as good as when stronger applications are used." In conjunction with this treatment

he sometimes uses 1 per cent ammoniated mercury ointment at night and washes it off in the morning with soap and water, then applying the lotion during the day

Sulfathiazole—Winer and Strakosch (1940) treated 60 patients by local application of 5 per cent sulfathiazole ointment, 1 ounce (30 Gm) of the ointment usually sufficing to effect a cure they said that not only is the treatment less disagreeable than the others but cure is also obtained in a considerably shorter time than with other types of treatment

TINEA VERSICOLOR

This malady is characterized by the presence usually only on the chest and shoulders of a yellow or brown macular eruption that sheds very fine scales There are usually one or more large plaques with numerous small lesions round about them Itching is slight or entirely absent The disease which is caused by *Microsporon furfur* is rather common among men but is entirely harmless A few cases involving the scalp have been reported in Europe and America a distribution which is said to be fairly common in the Far East

THERAPY

Tinea versicolor yields readily to frequent applications of a saturated solution of sodium thiosulfate (sodium hyposulfite) but only if the affected areas are first vigorously scrubbed with soap and water and then dried before making the application If the solution is also saturated with thymol it keeps indefinitely without the appearance of mold Crocker cited by Sutton has found the use of a 5 per cent solution of the thiosulfate followed by a 3 per cent solution of tartaric acid to be even more efficacious

ERYTHEMA MULTIFORME

This disease is characterized by the rather sudden appearance of red to violaceous inflammatory lesions that as the name implies are multiform they may be macular papular vesicular or bullous The sites of predilection are the face neck arms hands legs and feet Subjective symptoms are few or none but the attack usually lasts from two to three weeks and the same individual may be afflicted time and time again The etiology is unknown though many observers are inclining to the belief that this malady will eventually be placed among the allergic diseases i. e. that it is an allergic reaction to a drug or to some article in the diet Many men feel that the attacks are often due to a toxemia of intestinal origin

THERAPY

Inquiry into what drugs are being taken should be made arsenic mercury, the iodides and phenolphthalein seem to be the chief offenders Dieting and the taking of copious amounts of water are sometimes of value perhaps

the newer approach to food allergy might well be tried in recurring cases. At the New York Skin and Cancer Hospital we used always to give an initial dose of castor oil and then keep the patient on the Bulkley diet of rice (without sugar or cream), bread, butter, and water as long as he would cooperate—treatment that, plus the forcing of fluids, was thought to lessen considerably the duration of an attack. For local application, calamine lotion may be used (see Index). There is no evidence that any of the internal remedies that have been recommended are of any use.

EPIDERMOPHYTOSIS

(*Ringworm of the Hands, Feet, Groin, Axillae, Breasts and the Hairless Skin Generally*)

This is a skin disease that, in one form or another, most people seem to have. The name is objected to because the causative fungus, *Epidermophyton inguinale*, is found in perhaps only a third of the cases, such names as trichophytosis and dermatophytosis being offered as substitutes. However, French, German, Italian, and, I believe, most of the British dermatologists have adopted the name epidermophytosis, also the majority of Americans (Why must some men who should know better stoop to the vulgarity of "athlete's foot," the catch phrase of nostrum vendors?) The principal forms of the disease are the following: (1) vesicular, and (2) scaling, both of which predominate on fingers, toes, palms and soles, (3) macular, which is of two sorts, one (also called eczema marginatum or "jockey strap itch"), the well known red, definitely margined lesion occurring principally in the groin region, the axillae and beneath the breasts, and the other (*tinea circinata*), the slightly elevated, ringlike patches that occur principally on the face, neck and hands, and are spoken of as common ringworm of the body; and (4) macerated, the familiar lesion between the fingers or toes and beneath the breasts, presenting as an area of clean, white, sodden tissue of a varying degree of thickness. There are several other forms, less frequently encountered.

The disease is certainly contagious, but the problem of protecting against it, seeing its ubiquity and protean character, is a very difficult one indeed.

THERAPY

Treatment of epidermophytosis has never been entirely satisfactory, some cases resisting any and all sorts of measures, while others clear up very quickly under the simplest treatment (I distinctly remember cases, seen while working in Williams' clinic at the New York Skin and Cancer Hospital, that rapidly cleared up under the boric acid ointment being used at the time as a placebo). To attempt to list all the preparations in use against this disease would be hopeless, I shall therefore content myself with mentioning some of the remedies in use by White, of Boston, and appending a few other measures especially employed against the infections of the feet. Attempts to desensitize with gradually increasing amounts of the offending agent in the form of the preparation known as "trichophyton" are perhaps logical but they do not seem productive of significant results.

for example, Trauh and Tolmach (1935) gave the injections to a series of 135 patients and found that they had "little if any" effect on the course of the malady, these same workers, in 1938, also reported studies indicating that little was to be expected at present from convalescent serum or the vaccines currently in use

Vesicular.—After opening the deep vesicles antiseptically, apply any of the following ether, tincture of iodine, hot soaks of 1 per cent potassium permanganate solution, saturated solution of boric acid, 10 per cent alcoholic solution of trinitrophenol (picric acid), 0.4 per cent copper sulfate, or paint with

Oil of cinnamon	gr xx	1 2
Thymol	gr xlv	3 0
Alcohol to make	℥iv	120 0
or		
Ether	℥ss	2 0
Balsam of Peru	℥j	4 0
Collodion flexible	℥j	30 0

In the paper of Myers and Thienes (1925), in which the cinnamon-thymol mixture was first proposed, the original proportions were 2 per cent of oil of cinnamon and 5 per cent of thymol. The cinnamon oil is sometimes irritating, in which instance it should be omitted from the formula.

Moist or Macerated.—Crude coal tar may be used in from 6 to 100 per cent strength, as

Crude coal tar	gr xlv	3 0
Zinc oxide	gr xlv	3 0
Petrolatum to make	℥j	30 0

Or the *Lotio Nigra* ("black wash") of the National Formulary may be freely used, this is a preparation containing 8.75 Gm of calomel, 15 cc of water, and lime water to make 1000 cc

Macular and Scaling.—Whitfield ointments 1 or 2

Whitfield 1
Salicylic acid, 3 per cent
Benzoic acid, 6 per cent
Petrolatum to make

Whitfield 2
Salicylic acid, 6 per cent
Benzoic acid 12 per cent
Petrolatum to make

or any of the following

Salicylic acid	℥ss	2 0
Precipitated sulfur	℥ss	2 0
Lard to make	℥j	30 0
Mercurous chloride (calomel)	℥uss	10 0
Lard to make	℥j	30 0
Red mercuric sulfide	gr iiss	0 1
Salicylic acid	gr xx	1 2
Benzoic acid	gr xxx	2 0
Precipitated sulfur	gr xlv	3 0
Hydrous wool fat (lanolin)	℥j	30 0
Petrolatum to make	℥ij	60 0
Yellow mercuric oxide	gr ij	0 12
Petrolatum to make	℥j	30 0

This long and varied list signifies, says White, but one thing—a confession of therapeutic weakness. But he then adds that he has of late been using a 2 per cent aqueous solution of mercurochrome with most promising results. He swabs it on once a day and subsequently twice a day, permitting no bandages. At the appearance of small fissures the applications become painful and must be stopped until healing has taken place.

Treatment of Lesions on the Feet—It is customary to shift about among the above preparations, adding to the list fresh 3 to 5 per cent iodine and 1 per cent potassium permanganate solutions. The latter solutions may also be applied to mild vesicular lesions, but bullae should be aseptically opened and wet dressings of 1 part of solution of aluminum acetate and 15 parts of saturated solution of boric acid applied. Some cases, whether wet or dry, will stand no very irritating applications, for these the coal tar preparation of White seems best suited.

Francis (1941) melts phenol and rubs up 3 parts of it with 1 part of camphor until the mass is liquefied, this is then kept in a tightly-stoppered bottle and a small amount applied to the lesions (the preparation is caustic if applied to wet skin) once daily.

Taylor (1929) reported excellent results in a small series of cases in which he froze the lesions with the ethyl-chloride spray.

'To be effective freezing should produce blanching of the skin (including the lesion itself) for a distance of at least 0.5 cm. beyond the periphery of the affected area. The blanching should be sustained for from one half to one minute. In most cases one complete daily freezing of all lesions will suffice. Where the epidermis is thick as in the plantar region, it may be advisable to apply the treatment twice daily, and from two to six or more applications of the spray may be required to secure subsidence of the infection. Plantar lesions are protected by a slight dressing between treatments but digital and interdigital lesions are not. Loose skin edges and overhanging margins of epidermis are trimmed away to give more effective access to the spray.

Seldowitz (1940) has reported the satisfactory use of leather insoles containing rubber impregnated with 8-hydroxyquinoline, parachloromethyl enol and chlorthymol. 72 to 80 per cent of cures were obtained in 59 cases with demonstrable mycelia and in 100 per cent of 51 cases with demonstrable mycelia, it was necessary to use the insoles for two to four months.

Haggard et al. (1939) have reported chemical cure in 70 per cent of 37 patients treated by iontophoresis of copper during an average period of about five weeks; properly, they looked upon the report as merely preliminary in nature. Swartz (1939) is experimenting with the quantitative inhalation of ethyl iodide and reports good results, but it does not seem that the method is as yet applicable to the conditions of general practice.

Prehn (1938) had good success with the following powder used by 576 men in a destroyer division of the U. S. Navy, the effect being as good apparently in other types and locations as in the affections of the feet, the powder is rubbed in three times daily and then later at intervals as indicated.

Salicylic acid	5 Gm.
Menthol	2 "
Camphor	8 "
Boric acid	50 "
Starch	35 "

Prophylaxis.—Gould (1931) reported good results with a powder of 20 per cent sodium thiosulfate in boric acid, applied to the feet and inside the footwear after a bath, or night and morning. Goodman (1931) recommended the following powder, his laboratory studies having shown the advisability of previously sterilizing the infusorial earth:

Phenyl salicylate (salol)	gr xl	2 5
Chloral hydrate.....	gr xl	2.5
Purified infusorial earth (sterilized)		℥iv	120 0

Prehn (1938) has used the salicylic acid compound powder (see above) with good results in prophylaxis. For large-scale prophylaxis, as in gymnasia, public showers, etc., it is usual to employ in a compulsory footbath 20 per cent sodium hypochlorite diluted 20 to 1 and changed every second or third day.

Actual fumigation of the shoes may be accomplished by inserting in them a piece of blotting paper containing a teaspoonful of formalin, wrap tightly for twenty-four hours and air thoroughly for two days before wearing again. Birnbaum (1941) sprays the formalin into the shoes with an ordinary atomizer on three successive nights, allowing them to be worn after airing for eight hours. There is no need of destroying clothing, as materials of all sorts may be sterilized safely by first washing, then soaking in 1:1000 bichloride of mercury for a day, and afterward thoroughly rinsing in water before drying.

POMPHOLYX

(*Dysidrosis*)

This is a well-known affliction of many individuals during the hot summer months; its exact relationship to sweating is not understood, but significantly the lesions occur principally on areas where perspiration takes place freely—the lateral aspects of the fingers and toes, and the palms and soles. Pearly vesicles appear embedded in the epidermis, there is much itching, and occasionally large bullae are formed and usually quickly ruptured by scratching. *With the passage of the "hot spell," subsidence of the vesicular stage takes place but moderate desquamation and a yellowish-brown discoloration persist for several weeks.* In the soles and palms the vesicles usually lie very deep and make their presence known principally through the "shotty" feel they give to these regions.

THERAPY

Pompholyx may appear in an individual having epidermophyton infection or scabrous or other eczema, in which cases the treatment is merely that of the primary disturbance. In cases unassociated with other lesions and merely occurring when the individual sweats excessively, one should be very chary of applying the "strong" type of preparations used in epidermophytosis as they will often only aggravate these idiopathic cases. Indeed, it seems that the treatment most productive of results here is to do nothing and pray for cool weather.

RINGWORM OF THE SCALP

Ringworm attacks the scalp only in children. The patches are round and scaly, but not centrally involuted as in similar affections of the glabrous skin, they are not completely bald, but contain numerous brittle or broken hairs and dilated or "d(bris stuffed" follicular orifices. In the older patches there are usually many young hairs with fine shafts. In severe cases the whole scalp may be involved and the itching become quite intense.

THERAPY

Manual Epilation and Application of Antiseptics—This, the old treatment of ringworm of the scalp, requires anywhere from six months to three years to bring about a cure. The hair must be clipped short and maintained so, and the hairs in the affected areas plus those around the margins must be pulled out with the forceps. The scalp must be frequently and thoroughly washed with soap and water, and an antiseptic ointment, such as 10 per cent ammoniated mercury ointment, frequently applied over the surface (this ointment should be omitted, however, if iodine is to be applied later, unless it seems desirable deliberately to produce a dermatitis venenata). For application to the affected areas *per se*, the following are a few of the remedies used, they are all powerful irritants and are therefore to be employed with very great caution especially as regards keeping them out of the eyes.

Chrysarol in	℥j	4 0
Chloroform to make	℥ij	60 0
Careful!		
Chrysarol in	℥j	4 0
Petrolatum to make	℥ij	60 0
Careful!		
Tincture of iodine	℥ss	15 0
Alcohol to make	℥ij	60 0
(Some men use the tincture undiluted.)		
Iodine crystals	gr x	0 6
Thymol crystals	gr x	0 6
Oil of cinnamon	℥x	0 6
Petrolatum to make	℥ij	60 0
Crude coal tar	℥iiss	6 0
Zinc oxide	℥iss	6 0
Petrolatum to make	℥ij	60 0
Resorcinol	℥iss	6 0
Petrolatum (or glycerin) to make	℥ij	60 0
Whitfield 1 or 2 (see Epidermophytosis)		
Salicylic acid	℥j	4 0
Precipitated sulfur	℥j	4 0
Petrolatum to make	℥ij	60 0
Betanaphthol	℥ij	8 0
Precipitated sulfur	℥j	4 0
Petrolatum to make	℥ij	60 0
Salicylic acid	℥iss	6 0
Gentian violet	gr xviii	1 2
Alcohol to make	℥ii	60 0

X-ray Epilation—There is no longer any doubt that preliminary epilation of the entire scalp by the use of x ray, to be followed by the application of the antiseptics as above, is the best available treatment, but Lewis and Hopper (1937) hold that this method need not be resorted to if the infection is caused by fungi that are also pathogenic to animals (*i.e.*, chiefly *Microsporon lanosum* in contradistinction to *M. audouinii*). Wise says that in his extensive experience at the Vanderbilt Clinic, the hair has come out in from seventeen to twenty-one days after x ray epilation and regrowth has occurred within three months. However, I cannot refrain from cautioning the reader against placing his patient in the hands of just *any* upstart operator of an x ray apparatus, this is a special technic, and, like all special technics, requires study and practice in order to obtain mastery. It is not easy to forget the unfortunate sequelae of unskilled roentgen ray or radium therapy.

RINGWORM OF THE BEARD

The treatment of ringworm of the bearded region differs in none of its essentials from the treatment of ringworm of the scalp.

SEBORRHEIC DERMATITIS

This is probably the commonest of all skin diseases. In the scalp it is known as dandruff, which may be of the dry scaly or the moist greasy variety. In many cases lesions are also seen along the fringe of hair on the forehead, in the eyebrows, on the outer aspects of the nostrils and behind the ears. The most frequent site of predilection other than the points mentioned is the sternal region, here the lesions are rounded, irregular or circinate, and are covered with greasy yellowish scales. The differentiation between seborrheic dermatitis, ringworm of the glabrous skin and psoriasis is not always easy to make. There may be much itching.

THERAPY

The remedies for this condition are of course legion, which is simply an indication of the relative ineffectiveness of them all. However, any one of the following plans of treatment will lessen the severity of most cases, some will be "cured," though return of the lesions is almost certain. Many dermatologists feel that a fatty diet predisposes to this condition, and therefore rigorously restrict the intake of certain foods, I used to feel in a rather superior fashion that dieting for dandruff was too amusing to be taken with entire seriousness, but now, with the allergists almost daily enlarging their field, one can no longer be certain about anything. Other observers believe that a diet high in carbohydrate predisposes to this affection. Gross (1941) has reported some very interesting studies of the effect of liver extract

therapy in a group of cases showing seborrheic like lesions but not the frank syndromes associated with deficiency in the various fractions of the vitamin B complex, he does not claim curative effect of liver extract in ordinary seborrheic dermatitis.

Ammoniated Mercury and Salicylic Acid—These drugs, as in the following prescription, may be thoroughly rubbed into the scalp one or two nights a week, being washed out with soap and water the next morning

Ammoniated mercury	gr xiv	3 0
Salicylic acid	gr x	0 6
White wax	℥j	4 0
Hydrous wool fat	℥v	20 0
Petrolatum to make	℥ij	60 0

This contains 5 per cent of ammoniated mercury and 1 per cent of the salicylic acid, the quantities may be doubled giving 10 and 2 per cent respectively, but higher than this it is perhaps not advisable to go in the average case. On the nights when this ointment is not being used Sutton advises the employment of the following lotion, which he accredits to Johnston

Mercuric chloride	gr ½	0 01
Chloral hydrate	℥ij	8 0
Spirit of formic acid (N.F.)	℥iv	15 0
Castor oil	℥viii	0 5
Oil of bergamot to give odor		
Alcohol (80 per cent) to make	℥vi	180 0

Sulfur—This drug may be used in the form of a simple sulfur ointment as the following

Precipitated sulfur	℥j	4 0
White wax	℥j	4 0
Hydrous wool fat	℥v	20 0
Petrolatum to make	℥ij	60 0

or it may be somewhat reduced in amount and combined with salicylic acid as in the following, in which the salicylic acid may be doubled in amount if considered desirable

Precipitated sulfur	℥ss	2 0
Salicylic acid	gr x	0 6
White wax	℥j	4 0
Hydrous wool fat	℥v	20 0
Petrolatum to make	℥ij	60 0

Resorcinol—This drug is used either as ointment or lotion in the strength of 1 to 6 per cent, the following formulæ, much used in my day at the New York Skin and Cancer Hospital, contain 4 and 6 per cent, respectively

Resorcin	gr xx	1 2
Petrolatum to make	℥j	30 0
Resorcin	℥iv	15 0
Glycerin	℥j	30 0
Alcohol	℥vj	24 0
Water to make	℥viij	250 0

Dark hair is not appreciably affected by resorcin, but the fact should always be borne in mind that this drug will stain light, red or white hair, especially if the patient exposes the head to the sunlight after an application of the ointment or lotion. Resorcin monoacetate is said to be less apt to do so, it may be substituted for resorcin in equal amounts. A satisfactory prescription would be written by replacing the chloral hydrate in the Johnston formula (see above) by 5uss (10 0) of resorcin monoacetate

SYCOSIS VULGARIS

This is a chronic, discrete, pustular folliculitis of the bearded region caused by several strains of staphylococci. The essential lesions are either superficial or deep seated papules or pustules pierced by hairs that are easily pulled out. The infection may persist for many months or years and the resultant alopecia and scarring are sometimes quite considerable

THERAPY

Here, as in the ringworm infections, the nren must be epilated either by x ray or forceps, and the antiseptic and stimulating drugs applied in ointment or lotion for a long period of time. The reader is referred to the articles on ringworm of the scalp and beard, for I fail to follow the dermatologists in the fine distinctions they would have made in the treatment of the tinea and staphylococcic infections. X ray is said to cure about 40 per cent of cases. At the New York Skin and Cancer Hospital, Throne and Myers have obtained better results from nonspecific protein therapy (*methods in Asthma*). Others have had occasional success with bacteriophage

LICHEN PLANUS

This is an inflammatory disease of the skin that is usually subacute in its onset, though it tends to run a chronic course and to recur many times after spontaneous recovery or "cure." It is characterized by the appearance, principally on the flexor surfaces of the wrists and forearms and the inner aspects of the knees and thighs, of intensely itching glistening, red to violaceous, round angular or star shaped, plane topped, pinhead sized papules, at first these tiny papules, many in number, remain discrete, but they tend ultimately to coalesce into rough scaly patches. The disease not infrequently attacks the visible mucous membranes, other rare forms there are with which we cannot be concerned in this book. Lichen planus is a dry disease throughout its course, with pigmented areas or slightly atrophic spots being sometimes left behind after departure of the lesions

THERAPY

Despite the frequency with which this disease is seen in practice, very little advance in its treatment has been made in many years. White believes that the cure depends mainly on natural evolution and that treatment is therefore principally palliative, an opinion in which many observers concur. However, it is usual to give preparations of arsenic and mercury by mouth (the arsphenamines usually fail when injected) and to treat the pruritus locally; bismuth has latterly begun to have some successes to its credit also. Mercury and bismuth administrations are described in the section on syphilis, inorganic arsenic in the section on chorea. Some observers feel that the use of iron as in hypochromic anemia is of value especially when combined with the use of arsenic. Burgess (1941) has employed preparations containing the vitamin B complex with some success in a small number of cases. In the most stubborn cases, x-ray therapy is sometimes resorted to, but with variable results. Antipruritic measures are discussed at several places in the book, see Index.

PSORIASIS

Psoriasis is a common usually nonitching, nonpainful, inflammatory skin disease characterized by a typical course, a typical appearance, and a typical distribution. *Course* the disease usually develops between the ages of ten and thirty, persists for a variable period of time, disappears spontaneously, and recurs and disappears again many times throughout the patient's life. *Appearance* the lesions are papular, multiform, dry, reddish, and covered with white, gray or silvery imbricated scales. The scraping away of every one of the scales from a single papule reveals a very red, easily bleeding elevation, in long standing cases many of the papular lesions coalesce to form thickened patches covering surprisingly large portions of the body. In the intervals between attacks the skin usually clears entirely. *Distribution* the eruption is symmetrical and from a beginning usually on the elbows and knees, may spread all over the body, the scalp is often involved, but the face and the backs of the hands are frequently spared even when the involvement elsewhere is very extensive.

Psoriasis is generally considered to be rare in the Orient and in the tropics, but Pardo Castello (1934) says that it is of frequent occurrence in whites residing in Cuba, whose climate is subtropical. Most patients in the temperate zones are better in the summer and worse in the winter. The disease is extremely rare in full blooded Negroes and American Indians. Nothing is known of its etiology or of what part, if any, heredity plays in its causation. In Lane and Crawford's (1937) series of 231 patients, about five times as many were overweight as were underweight—I wonder how this compares with the weight status of nonpsoriatic individuals in the same age groups? Treatment of psoriasis was probably described in the Papyrus Ebers, which was written about 1550 B.C.

THERAPY

While there are many cases of psoriasis that remain completely intractable ('an antidote for dermatologists' ego'—Bechet, 1936), the duration of the average moderately severe attack can usually be much lessened by proper local treatment. X ray therapy sometimes causes temporary improvement, but the occasional good result would seem to be bought at an excessively high price, to wit prolonged treatment, such as is necessary in this disease, practically always lowers the white blood count more than can be entirely safe, if it is unskillfully applied, the patient may be seriously burned, and the treatment may superimpose upon the lesions an itching, burning dermatitis. The use of autoserum, intravenous foreign protein, intramuscular injection of a suspension of the patient's own scales, low protein diet, low fat diet, hypocalcemia, venesection, autohemotherapy, x ray stimulation of the thymus gland—all these measures have had their occasional successes, but I think that such results are utterly without significance in a disease so variable as this. The internal remedies recommended are legion, but the only one in which dermatologists return after their dallings with other drugs—if they return at all—is arsenic. It is usually begun at 1 to 3 drops of Fowler's solution (U.S.P. solution of potassium arsenite) three times daily, and increased 1 drop per dose every other day until 10 drops are being taken after each meal, this dose is maintained for a week or ten days unless signs of slight poisoning supervene earlier, i.e., puffiness under the eyes or about the ankles, or gastro intestinal disturbances. It is not commonly realized that arsenical neuritis can also be produced with this method of administration. The best practice is perhaps to rest the patient for a while after he has been held the week or ten days on the full dose but some practitioners gradually reduce the dose and thus bring him back again by gradations to a nonarsenical basis. There is nothing to indicate that arsphenamine, or any of the other organic arsenicals, has any value here. Gold and manganese have both had a trial but one hears little of them nowadays. Of course the latest agents to have a vogue are the sulfonamides and vitamins, especially vitamins B, C, D, and P, there have been some good results of course because psoriasis is capricious and will respond at times to almost anything or again to nothing at all. I think the most important recent report is that of Madden (1940), who treated 112 patients with the following agents: vitamin D, vitamin B₁, vitamin B complex, brewer's yeast, vitamin C, liver extract, diluted hydrochloric acid, estrogenic substance, sulfanilamide, bismuth salicylate, anterior pituitary extract or adrenal cortex extract alone or in combination with one another or in combination with a low fat diet. No results which one could by any means call impressive came out of this study—Madden's treatment of choice remained a low fat diet plus vitamin B, and some sort of exfoliating ointment.

A standard treatment is to send the patient south, but he is not likely to benefit greatly by a mere sojourn in a warm climate unless the body is freely exposed to the sun.

In the local treatment of psoriasis it is very essential that all the scales be removed before applying the remedial agent. This is usually accomplished by vigorous scrubbing with soap and water in a warm alkaline bath, but there are a few individuals who are made worse by the contact with water, for these, recourse must be had to the "grease bath," i.e., the scrubbing

of the body with some such preparation as the following which is then to be thoroughly wiped off before applying the curative preparations

Hydrous wool fat (lanolin)	℥v	20 0
Glycerite of boroglycerin	℥ij	60 0
Petrolatum to make	℥iv	120 0

The following preparations are perhaps those most used in treatment the majority of cases will respond to any one of these, but in some cases the whole gamut will have to be run. All of these ointments should be worked into the lesions with a stiff toothbrush, but they are not to be applied to other than diseased areas.

Ammoniated Mercury and Salicylic Acid—For treatment of the scalp and face a combination of these drugs is employed as chrysarobin and the other irritants will ultimately get into the eyes when used as long as is necessary in psoriasis. The formula below contains 2 per cent of salicylic acid and 10 per cent of ammoniated mercury, the former may be increased gradually to 5 per cent and the latter very cautiously to 20 per cent, in rare instances both are carried much higher than this.

Salicylic acid	gr xl	2 4
Ammoniated mercury	℥ j	12 0
White wax	℥ j	9 0
Hydrous wool fat	℥j℥ij	40 0
Petrolatum	℥iv	120 0

Chrysarobin in Ointment—This drug is undoubtedly effective in more cases than is any other, but it is extremely disagreeable to use as it stains everything brown. The stains are only partially removed from linen by the use of a chlorinated lime solution. Also the drug may at any time especially on the upper ranges of its effective concentration produce a dermatitis that is sometimes very aggravating. It is usually begun at 5 per cent strength and cautiously increased to 25 or even 35 per cent, though few cases will stand this latter concentration. The formula contains 5 per cent.

Chrysarobin	℥iss	6 0
Petrolatum	℥ij	60 0
Hydrous wool fat to make	℥iv	120 0

Dioxyanthranol (Anthralin), introduced on the Continent a few years ago as cignolin, is chrysarobin minus a methyl group in the formula. It is reputed to be much stronger than chrysarobin, according to Beerman *et al* (1935) of Philadelphia, the effective range of concentration is between 0.1 and 1 per cent. The advantages claimed for it are that it does not have chrysarobin's propensity for causing kidney irritation upon being absorbed, that it does not cause extensive dermatitis and may be used on the face without causing conjunctivitis and that it discolors neither the clothing nor hair so much as does chrysarobin. The indications are that this new drug is fully as effective as chrysarobin, but there have not as yet been published sufficient studies of it to make the point certain by any means. In the concentrations above stated it may be substituted for the classical drug in any of the following formulae.

Chrysarobin in Collodion, Gutta-Percha or Gelatin Film—The drug may be prescribed in any one of these media to be painted on, a method more acceptable to the fastidious patient but less effective than the use in ointment, the gutta percha formula is to be preferred, as chrysarobin is not soluble in collodion. The formulae contain 6 per cent, to be increased just as in the ointment.

Chrysarobin	℥ss	2 0
Collodion (not the flexible) to make	℥j	30 0
Chrysarobin	℥ss	2 0
Solution of gutta percha (N F IV) to make	℥j	30 0

or the following may be written

Chrysarobin	℥ij	8 0
Soft glycerogelatin (N F) to make	℥iv	120 0

Such a gel is melted and applied with a brush and covered with a bandage. Some physicians prefer the zinc oxide paste for vehicle

Chrysarobin	℥iss	6 0
Zinc oxide	℥j	30 0
Starch	℥j	30 0
Liquid petrolatum to make	℥iv	120 0

Tar.—The following are forms in which this substance is frequently applied

Tar ointment (U.S.P.)	℥j	30 0
Petrolatum to make	℥iv	120 0
Oil of cade (U.S.P.)	℥j	30 0
White wax	℥ij	8 0
Hydrous wool fat	℥j℥ij	40 0
Petrolatum to make	℥iv	120 0

Chrysarobin, Tar and Salicylic Acid—A compound sometimes successfully used during my time at the New York Skin and Cancer Hospital had the following formula

Rectified oil of birch tar*	℥ij	12 0
Salicylic acid	℥vj	24 0
Chrysarobin	℥vj	24 0
Anhydrous wool fat	℥j	30 0
Soft soap to make	℥iv	120 0

Coal Tar—Coal tar is often better borne than the wood tars, it may be substituted in any of the above formulae. Goeckerman (1931) has seen some indications of hastened recovery if ultraviolet radiation to the point of tanning is carried on in conjunction with the coal tar treatments. The lesions are wiped practically clean of the ointment and the light then directed onto the skin through a thin film of remaining ointment, the belief being

* In the interest of simplification of our armamentarium, I see no reason why this preparation, the beloved *Oleum rusci* of the dermatologists, could not in all instances be replaced by the oil of cade, a U.S.P. preparation from which it surely can differ only slightly, if at all, therapeutically

that some new chemical substance, powerfully antipsoriatic, may be formed in the coal tar thus treated. Lesions are not re-treated with ointment until several hours after the daily light treatment. This type of management is enjoying some present vogue among dermatologists.

Unna's Chrysarobin-Ichthyol Compound—This much used preparation is variously written, but I believe the following formula to be the one most often employed.

Chrysarobin	℥iss	6 0
Salicylic acid	℥r xlv	3 0
Ichthyol	℥iss	0 0
Petrolatum to make	℥iv	120 0

Resorcinol—This drug is used in ointment in the strength of 5 to 10 per cent. the formula contains 5 per cent.

Resorcinol	℥iss	6 0
Petrolatum	℥ij	60 0
Hydrous wool fat to make	℥iv	120 0

Pyrogallol (Pyrogallie Acid)—This drug is used in ointment in the strength of 5 to 10 per cent, the formula contains 5 per cent.

Pyrogallol	℥iss	6 0
Petrolatum	℥ij	60 0
Hydrous wool fat to make	℥iv	120 0

Pyrogallol stains tissues and clothing black and is too irritating to employ about the eyes or genitalia. A greater objection to its use, however, is the fact that it may suddenly be absorbed in sufficient quantities to cause serious systemic poisoning. In rapid cases there are cyanosis, dyspnea, convulsions and collapse, but in the slower cases chills, diarrhea and vomiting, acute nephritis with dark scant urine, and sometimes jaundice and glycosuria, are the outstanding symptoms. The indications are to empty the gastro intestinal tract with emetics and purgatives, apply heat to the body, and stimulate, there is no specific antidote.

Betanaphthol—This drug is probably less effective than pyrogallol, but it is also less dangerous, systemic poisoning of the phenol type may occur, however, from absorption through the skin, though the recorded cases are few. It is used in ointment in the strength of 5 to 10 per cent, the formula contains 10 per cent.

Betanaphthol	℥iij	12 0
White wax	℥ij	8 0
Hydrous wool fat	℥jssj	40 0
Petrolatum to make	℥iv	120 0

or the following peeling paste of the N.F. may be applied for a short time twice a day.

Betanaphthol	℥iss	6 0
Precipitated sulfur	℥j	30 0
Petrolatum	℥iij	12 0
Soft soap to make	℥ij	60 0

LUPUS ERYTHEMATOSUS

Lupus erythematosus is a chronic inflammatory skin disease characterized by the insidious development of small, pink, dry, macular patches with grayish adherent scales, which patches, both by extension and coalescence, form well-defined, thickened areas, varying in size from a small coin to the palm of the hand or more, and having in their center one large or several small thin, colorless or whitish, atrophic scars with gaping follicular orifices. The sites of predilection of this disease are the scalp, the regions about the ears, the cheeks, and the bridge of the nose, perhaps the next most frequent sites are the backs of the hands. The mucous membranes are involved in about one fourth of the cases. When the lesions occur on both cheeks with a connecting bridge across the nose, the most typical distribution of all, the "butterfly appearance" is often glibly referred to—an unfortunate designation, for certainly in the vast majority of cases these patches resemble no butterfly ever seen or heard of.

The etiology of this malady is entirely unknown. The cases usually begin between the fifteenth and thirtieth years and run an erratic course throughout the rest of the patient's life, though spontaneous disappearance sometimes occurs. There are no constitutional symptoms and the patient's welfare is disturbed only insofar as the unsightliness of the affliction alters his or her environmental reactions. The acute disseminated variety of the disease, with its severe general symptoms and grave prognosis as to life, is too rare to concern us in this book.

THERAPY

Local Treatment—X-ray, radium, carbon dioxide snow, ultraviolet light, high frequency current—all these agents have more failures than successes to their credit, though instances of brilliant results with any of them may be cited. So, too, it is with the local application of drugs. I list below the remedies most frequently employed, but can only say that they have been found one and all to be sadly lacking in ability consistently to produce the kind of results that are occasionally reported following their use.

Sulfur—This drug is usually applied once or twice daily in ointment, the formula contains 4 per cent, but it may be increased in strength

Precipitated sulfur	gr xx	1 2
Petrolatum to make	3j	30 0

Sulfur and Salicylic Acid—These drugs are used in combination to be applied in ointment once or twice daily, or alternated with the sulfur alone, the formula contains 4 per cent sulfur and 10 per cent salicylic acid, both of which may be gradually increased

Precipitated sulfur	gr xl	6 0
Salicylic acid	3ij	12 0
White wax	3ij	8 0
Hydrous wool fat	3j3ij	40 0
Petrolatum to make	3iv	120 0

Lotio Alba—This is a mixture of sulfured potassa (U S P) and zinc sulfate, usually applied once or twice daily. The following formula is for

the mild form of the lotion, with which the treatment is usually begun, for a full description of the use of this *lotio alba*, see Acne

Zinc sulfate	℥ij	8 0
Sulfurated potassa	℥ij	8 0
Water to make	℥iv	120 0

Ichthyol—This drug is applied once or twice daily in ointment or collodion in 10 per cent strength

Ichthyol	℥ssiv	3 0
Petrolatum to make	℥j	30 0

or

Ichthyol	℥ssiv	3 0
Collodion (not the flexible) to make	℥j	30 0

Phenol—Pure liquid phenol is washed over the lesions once a week with a cotton applicator

Phenol-Lactic Acid—The following mixture is applied with a glass rod over the surface of the lesions once every ten days to two weeks phenol, 1 part, lactic acid, 4 parts The parts should first be cleansed with ether

Trichloroacetic Acid—This substance is painted on the lesions with a cotton applicator once a week, the parts having first been cleansed with benzine to facilitate penetration

Arsenic—Equal parts of arsenic trioxide and acacia are made into a paste with a saturated solution of cocaine hydrochloride and spread over the diseased area, though no more than a square inch at a time should be treated The paste is allowed to remain in place for twenty four to forty eight hours, when the slough is removed by poulticing

Pyrogallol (Pyrogallic Acid)—This substance is applied in ointment twice a day to small areas for two or three weeks, the sloughs being removed from time to time by poulticing, the formula contains 20 per cent, but this strength is sometimes doubled

Pyrogallol	℥iss	2 0
Rosin cerate	℥iv	15 0
Petrolatum to make	℥j	30 0

Quinine and Iodine—The patient is given 7½ grains (0.5 Gm) of quinine sulfate three times daily for five to seven days, during which time the lesions are painted with the tincture of iodine once each day, after a week, during which the crusts are removed either spontaneously or by poulticing, another course of treatment is given

Gold Salts—Gold salts of the type of Møllgaard's "sanocrysin," which have failed to win much support for themselves in the treatment of tuberculosis seem to have found a place in the treatment of lupus erythematosus At present in the United States, gold and sodium thioarsenate is the most extensively used preparation, though all those employed in Europe (triphal and krysoigin, principally) have their advocates here also In matters of dosage, reactions and results there are probably no differences of note now that all the more toxic salts are no longer used

Results—As with all new therapy, enthusiasm ran high in the beginning, but it has now considerably abated Schamberg and Wright, who introduced

gold and sodium thiosulfate treatment in this country, reported in 1936 on the results of their use of the drug intravenously in 70 patients during the preceding ten years. Of this number, 37 per cent were regarded as cured, 34 per cent greatly improved, and 17 per cent moderately or slightly helped. Of those regarded as cured, 2 had been well with no relapse for seven years, 2 for six years, 2 for five years, and 3 for four years. One or more relapses were suffered by 17 per cent of the patients after being partially or entirely free from lesions, some responded again to treatment, others were too discouraged to continue therapy. In Callaway and Stokes' (1938) series of 31 patients, 74 per cent suffered from one to four relapses after apparent cure.

Dosage—Schamberg and Wright did not give more than 25 mg as initial dose, 50 mg as second dose, and 100 mg as subsequent dosage, in the following instances, however, they varied this routine: (a) in cases of active inflammatory disease the initial dose was only 5 mg, and (b) in a few cases it was necessary to increase dosage to 200 or even 300 mg in order to obtain therapeutic effect. The injections are given weekly. A good many men proceed more slowly than this, witness the methods of Driver and Weller (1931): (a) an initial dose of 10 mg, followed one week later by 20 or 25 mg and increased 10 mg per week up to 50 mg, (b) in resistant cases the maximum dose is cautiously increased to 75 mg and occasionally to 100 mg, (c) ten weekly injections with a rest period of four weeks between courses continued until success or failure is apparent, the giving of as many as 100 to 150 injections to a patient has been several times reported, (d) if treatment is continued after untoward symptoms have developed, drop to 5 mg or less and carefully determine patient's tolerance.

Monash and Traub (1931) reported on successful local injections not giving the drug intravenously but instead injecting into the diseased area either intradermally, subcutaneously or under the mucosa, 10 to 25 mg in 1 per cent concentration, with the addition of 0.25 per cent novocain. The slight swelling is controlled by cold applications. Alden and Jones (1936) say that their best results with the subcutaneous method were had in those patients who were able to get 10 mg regularly three times a week.

Reactions—The immediate reactions consist in (a) the anaphylactic type much like the nitritoid reaction to the arsphenamines, (b) mild febrile reactions with malaise and headache, which may last a few hours to several weeks, (c) metallic taste in mouth. The delayed reactions usually occur after the second or subsequent injection and may last only a few hours to several weeks: digestive disturbances, stomatitis and gingivitis, albuminuria, hepatitis and jaundice. Purpura, agranulocytosis and aplastic anemia have all been caused by the gold preparations. Skin reactions may be very serious, such as fatal exfoliative dermatitis. Focal reactions of the Herxheimer type also occur in the lesions, there are numerous unusual types of skin reaction which cannot be described here. Schamberg and Wright say that pruritus and scarlatiniform rashes are the most common manifestations of toxicity, the former being accepted as a warning sign and calling not only for temporary cessation of treatment but for the immediate beginning of sodium thiosulfate injections: 1 Gm in 10 cc of water and if dermatitis develops, to be repeated every other day for the first week and then continued at weekly intervals until the skin clears. Barber (1929) recommended dextrose injec-

tion Throne *et al* (1932) felt that increase in blood sugar and decrease in chlorides and urea nitrogen are early signs of impending reaction

I am unable to form an opinion from the literature just what the percentage mortality is with the use of gold salts, though it is nowadays certainly very much lower than the 18 per cent stated by Würtzen some years ago Schamberg and Wright attributed death to the use of the drug in only 2 of their patients, which is not quite 3 per cent and probably as low as can be claimed Certainly the compounds should be employed only with the greatest care It would seem that the definite contraindications to their use, generally agreed upon, are disorders of kidneys, liver or spleen, active tuberculosis anywhere in the body, evidences of a lowered resistance, pregnancy, acute lupus erythematosus disseminatus, severe gold reactions I should think that no patient with a purpuric tendency should receive the gold salts and that, considering that agranulocytosis has been caused by these salts, constant watch should be kept upon the white blood cells during their administration, it does not seem to me, however, that the published data of Weiss *et al* (1937) quite conclusively show that the leukocyte level alone can be used as a guide to therapy Throne counseled the removal of any discoverable foci of infection before instituting treatment with gold

Bismarsen —Weiss *et al*, at the end of 1941, reported 28 cases treated with this drug (for details regarding the use of bismarsen see Syphilis) with results which indicated to them the value at least of further experimental studies

Sulfonamides.—These drugs are being used of course and there is enthusiasm over the results in some quarters, but the fact that many failures as well as successes are being recorded indicates that as yet we know only that the long hoped for specific in lupus erythematosus has not been found According to Barher (1940) the reactions to the sulfonamides are of frequent occurrence in this disease and of peculiar nature and violence

Liver Extract.—It may be worth mentioning that King and Hamilton (1941) were very pleased with the result of employing intramuscular injections of liver extract in 6 of their 8 patients

ECZEMA-DERMATITIS

There is a large group of maladies characterized histopathologically by an identical process of spongiosis The occurrences are erythema, intercellular epidermal edema, microscopic and later macroscopic vesiculation, with or without the appearance of small isolated subvesicular papules The lesions weep when the vesicles rupture and encrust when the high fibrin exudate coagulates, scaling occurs if the keratinization process is much interfered with, and continued inflammation causes the skin to lose its elasticity and thicken with exaggeration of the normal lines (lichenification) Dermatologists are intensively seeking to simplify the very puzzling nomenclature of this group, but it seems to me that for the man in general practice who has had no specialized dermatologic training, the most profitable course is to consider any case in which the gross lesions more or less comply with

the above brief description as one belonging in the "eczema-dermatitis" class. All such cases have an identical therapeutic approach, *i e*, each needs to be investigated from the standpoint of the "general considerations" presented below, and some will require the 'local treatment' described further on.

THERAPY

GENERAL CONSIDERATIONS

The Metabolic and Endocrine Factors—It is now apparent after a good many years of exhaustive and expensive research that there are no metabolic and endocrine disturbances underlying eczema-dermatitis with any significant regularity. Therefore routine blood chemistry and basal metabolic studies are probably not justified, nor is the routine administration of glandular products, or of calcium or any of the alteratives. Evidences are being found of local disturbances of metabolism in the skin but they are not such as can be determined by study of the general functions.

The Neurogenic Factor—These dermatoses rarely heal in persons whose emotional apparatus is being often battered, for, as Sack pointed out, a number of years ago, the skin occupies perhaps the largest single place in consciousness and has the widest and most varied sensory appeal and the richest vasomotor and other nerve supply in the body. Well does Stokes say, 'A mycosis may even be influenced by the stock market, and eczema by a course in French.'

The Allergic Factor—The importance of allergy in the causation has come to be generally recognized, indeed Bloch and his school are maintaining that all cases are allergic in origin, but I think that not many observers are as yet willing to go that far. It is nevertheless certain that a most thorough search for the possible allergic factor should be made in every instance. Poison ivy, primrose, ragweed, hair and fur dyes, inks (the Sunday rotogravure section), face powders, and a host of other domestic and industrial substances are already convicted, as are also a number of foods. Sensitization studies are often very difficult and the manifestations quite fickle in these cases, sometimes being present and at another time being absent, or sometimes being present but apparently without significant relationship to the symptoms. Possibly the allergic response goes up and down with the responsiveness of the sympathetic nervous system to fatigue and irritation, as Stokes asserts so that a patient who cannot wear a certain fur jacket this season but can do so the next may not be putting us to shame at all, but rather showing conclusively how much the allergic state is bound up with other affairs, perhaps our perky Miss by flaunting her coat flouts those stubborn fellows only who will see merely the immunologic phases of the subject.

The reader must turn back and study the subject of allergy, its detection and methods of treatment. The dermatologic phases are being particularly well presented by Sulzberger, the especially interested reader is referred also to the review of Stokes and Garner—see Bibliography for a list of all these papers. The usual injective methods of desensitization have upon the whole been disappointing in the skin cases; the withholding of convicted foods is much more often rewarded by instant improvement.

In the approach to the very difficult problem of infantile eczema-dermatitis, all the food constituents have had their day of shame, but all save

only the proteins have been able to raise their heads again. The early theory that fat intolerance underlay many cases was never really borne out by any subsequent investigations and it seems that it was given the coup de grâce by the failure of eczema-dermatitis incidence to drop coincident with the fat deprivation of the recent period of economic distress. The rather converse view of Hansen, that there is actually a deficiency in serum lipids, won some substantiation through the experiences of Cornbleet (1935) in feeding unsaturated fatty acids but Taulh and Zakon (1935) failed to confirm the findings, and it therefore seems entirely likely that this sort of treatment is scooting fast toward limbo despite the manufacturers' mumbo jumbo for linseed and maize oils. A few babies with mushy, odorous (pig pen) stools and a pronounced blue reaction to the iodine test will improve when the starches are greatly restricted, and the ones with acid, green, loose stools will be helped by sugar restriction, but it is quite likely that such digestive disturbances only serve to make easier the wrong kind, or rate, or whatnot of protein absorption from the intestine. However, that there is oftentimes an intimate relationship between infantile eczema-dermatitis and protein sensitization has been several times reaffirmed since Blackfan first pointed it out, in 1910. The chief offenders seem to be egg white, wheat, milk, oranges, oats, in about that descending order.

Unfortunately, however, the identification of the offending substance does not necessarily mean that its withdrawal will cure the disease. I have seen no report showing better results than those of Smyth *et al.*, in 1931, who obtained spectacular relief with dietotherapy alone in only about 20 per cent of their large series, 32 of the 47 successfully treated cases were from the test-positive group, and 15 from the group with negative skin tests. In 18 additional patients the diet was shown to be decidedly a factor though not the only one—15 gave skin reactions and 3 did not. The degree of reaction is by no means indicative of the part played by the sensitization, for, as Hill (1931) has well remarked, no infant who has the hyperacute type of sensitization is likely to have eczema, for the ingestion of the offending protein makes him so immediately ill that it is quite obvious what is causing his symptoms and the food is immediately removed from the diet. On the other hand it is quite possible that a sensitization may be too slight to give a positive test and yet be enough to cause eczema-dermatitis, for instance, those cases that give a negative test to cow's milk and clear up nevertheless at once when this is removed from the diet. The large proportion of infants giving positive tests to egg white in all series studied to date has been a puzzling observation, for in most of them egg has usually not yet been included in the diet.

Hill and Stuart (1929) developed an easily available and digestible milk-free food for use in cases of milk sensitiveness. The product, which is known as Sobee, is composed of soy bean flour, barley flour, olive oil, sodium chloride and calcium carbonate. It contains adequate amounts of the necessary minerals and of vitamin B, but must be supplemented by orange juice and cod liver oil for the other vitamins. Six level tablespoonfuls of this food are added to 7 ounces of water, 1 fluidounce of the mixture containing 17 calories. Unless the stools are loose, Hill adds a level tablespoonful of a mixture of maltose and dextrin to this mixture, which raises the carbohydrate percentage to approximately 7. Hill uses the Sobee in

all cases in which there is a positive skin test to milk protein or in very severe cases even if the test is negative, in all others evaporated milk is used. He discontinues it if no improvement has occurred in two weeks, he has been successful in about half the cases, but he says (1933) "If the eczema is due to milk, it will be cured with Sobee feeding." Smyth *et al* have found some infants unable to take Sobee, apparently because of sensitiveness to barley. Hill (1941) also finds that a great disadvantage of Sobee in some instances is that it causes large loose bowel movements and irritated buttocks. Latterly Hill has been experimenting with a mixture, not yet commercially available at the time of his report, which contained amino acids 20 per cent, dextrimaltose 42.3 per cent, virgin olive oil 18 per cent, arrow root starch 10 per cent, mineral salts 6.7 per cent, and only the small amount of protein contained in the 3 per cent of added brewer's yeast powder, he felt that in some cases this mixture had advantages over Sobee but found its chief fault to be its strong taste which caused some infants after a little while to refuse to take it.

Many pediatricians have observed that the boiling of milk for four to six hours, the prolonged boiling of all foods, or the substitution of evaporated or dried milk are often helpful measures. However, Rattner (1935) has pointed out that not all evaporated milks are subjected to the requisite amount of heat in their processing, and he therefore advocates the vigorous boiling of evaporated milk for several minutes before use. Vitamin C in the form of fruit juices is required to supplement boiled milk. A standard brand of evaporated goat's milk is also used with advantage.

Desensitization to milk is attempted by Rattner, who begins with drop—or even a fraction of a drop—doses of cow's milk daily by mouth, increasing the quantity so slowly that normal amounts will not be reached until six to nine months have passed. Individuals thus desensitized are said to require to take milk continuously throughout their lives to retain the immunity.

Focal Infection as a Factor—It is a very definite clinical impression that a focus of infection somewhere in the body has a very deleterious influence on eczema-dermatitis. Obviously, every effort should be made to eradicate foci, but bearing in mind the 'high strung' nature of many of these patients the pursuit of the elusive foe must be made with the utmost calmness and even leisure.

Types of Skin—The person with the dry, ichthyotic, parchment like skin will be better in summer or in warm climates because of the increased sweating, but the prognosis in him is unfavorable for the reason that his type of skin is definitely hereditary and so he begins his eczema-dermatitis career with a tendency which is incurable. He needs to avoid soap and to use greases plentifully, tends to become easily infected, and should probably not be given roentgen therapy, "which makes a bad matter worse by causing glandular atrophy." In the opposite type, the person with an oily, seborrheic tendency, Stokes feels that there is a definite indication for reduction of carbohydrates in the dietary, since the process is probably closely bound up with the carbohydrate storage mechanism and metabolism in the skin. In these cases the scalp, which is always concerned in the seborrheic process, must be treated, sulfur will be found to be almost specific when properly used, and there is a definite indication for the use of the roentgen ray to reduce

the activity of the sebaceous glands. Prognosis is better than in the ichthyotic type.

A good ointment for use after the bath by persons with excessively dry skin is the following:

Hydrous wool fat.....	3v	20.0
Glycete of boroglycerin	3ij	60 0
Petrolatum to make	3iv	120 0

As a substitute for soap, Lane and Blank (1941) offer a mixture which I present in prescription form below:

R	Sulfonated olive oil	3ij	60 0
	Sulfonated teaseed oil	3ij	60.0
	Liquid petrolatum	3iv	120 0
	Water to make	0j	500 0
	Label Use as soap substitute		

Pyogenic and Mycotic Factors.—Pustular complications point to the necessity to employ mild wet antiseptic dressings and later ammoniated mercury ointment, beginning with not above 1 or 2 per cent concentration. X-rays are to be used cautiously but ultraviolet radiation may be of some value. Those who are investigating the metabolism of the skin feel that here also the carbohydrate intake should be reduced. With regard to the mycotic factor, it can only be said that undoubtedly many cases of so-called "epidermophytosis" are really eczema-dermatitis, and conversely that some cases of eczema-dermatitis have a mycotic factor which is uppermost. Certainly many cases of epidermophytosis that are resistant to the ordinary treatment will be found upon careful restudy to have become eczematous, particularly beyond the borders of the original mycotic affection, and are being aggravated perhaps by the application of strong keratolytics.

LOCAL TREATMENT

Early Stage.—In the vesicular stage the use of wet dressings is the method of choice. They should not be applied with an occlusive covering, such as oiled silk or paper, but in such way as to gain the additional soothing and antipruritic effect of evaporation. Potassium permanganate is acceptable in 1 : 15,000 to 1 : 10,000 strength; the formula contains approximately 1 : 8000.

Potassium permanganate .	..	gr j	0.06
Water to make	0j	500.00

Of course saturated solution of boric acid may also be used, but the permanganate solution is not apt to become excessively irritating if inadvertently allowed to dry, as the boric acid may occasionally do. Lead and aluminum acetates are also much used because they are astringent and tend to lessen exudation, and are also to some extent antipruritic, but they are often too irritating to be borne by acutely inflamed tissues. The diluted solution of lead subacetate of the N.F. was deleted from the U.S.P. because too weak for most purposes; it is best to write for U.S.P. solution of lead subacetate and direct the patient to dilute it with 10 to 20 parts of water. The solution of aluminum acetate (N.F.) is to be diluted with 5 to 10 parts

of water Abramowitz feels that full strength alcohol should be more often employed for wet dressings when there are no open lesions

In excessively itching cases the alkaline colloid bath is often helpful Fill the tub half full with water just at body temperature, add a cupful of sodium bicarbonate, and then place in a cheesecloth bag 3 cupfuls of previously boiled oatmeal, and squeeze it in the bath until the water becomes opalescent Such baths may be taken for ten to twenty minutes several times daily Afterward the patient is to be patted dry and may have a boric acid, or the official rose water, ointment lightly applied, or the body may be powdered In some patients, 1 quart (1 liter) of vinegar to the tub of water has antipruritic effect

Some patients do not bear wet dressings well and must be treated with such lotions as will coat the lesions, or perhaps even with powders The N F calamine lotion

Prepared calamine	℥j℥iiss	40 0
Zinc oxide	℥j℥iiss	40 0
Glycerin	℥iiss	10 0
Solution of calcium hydroxide to make	℥j	500 0

coats well but will crust if allowed to dry too much between applications, it is to be removed with sweet oil, not water, or with the oil and egg yolk method of Glaze thoroughly and gently work oil into the skin and then add a small quantity of egg yolk (one yolk will serve for twenty or thirty cleansings if used economically), and briskly work up an emulsion, the addition of a few drops of water helps Rinse in cool water In some patients the amount of inert powder in the calamine lotion makes it too drying and irritating, but they will often find a mixture of the lotion and sweet oil in equal parts very soothing

A simple powder for dusting on dry or wet lesions is the following

Boric acid	℥ij	8 0
Zinc oxide	℥j℥iiss	40 0
Talcum to make	℥iv	120 0

The substitution of salicylic acid for the boric acid, in equal quantity, will make the powder antiseptic, but of course such a mixture must be used with extreme caution on acutely inflamed lesions A menthol boric acid combination, with talcum to make it stick, is often remarkably antipruritic

Menthol	gr xl	2 5
Boric acid	℥ij	60 0
Talcum to make	℥iv	120 0

Sometimes before using such a powder it is of advantage to sponge the affected area with hot sodium bicarbonate solution and then apply the powder after merely mopping off the solution.

For more active antipruritic effect, 1 to 2 per cent each of phenol and menthol may be added to the calamine lotion, but of course open or very acutely inflamed lesions contraindicate this application

In some acute cases, particularly of infantile eczema-dermatitis, White's crude coal tar ointment may be used from the very beginning, taking care

that the preparation is made according to the corrected formula, and that a properly prepared tar is used:

Crude coal tar.....	5ss	2.0
Zinc oxide.....	5ss	2.0
Petrolatum.....	5j	20.0

The crude coal tar is often used full strength as a paint, particularly for application to the cheeks and the resistant lesions behind the ears. With infants also it is nearly always necessary to prevent scratching; tying the wrists and ankles loosely to the sides of the crib is usually found to be the best method. A light masturbation splint, applied just above the knees, will effectively prevent rubbing with the feet. Wool should not come in contact with the body, and in some cases it is best to dress only in a diaper in a draped crib with an electric hulk to keep it warm. Pilcher wrote as follows of epinephrine to relieve the excessive itching: "The hypodermic dose was from 0.1 to 0.3 cc. of the 1 : 1000 solution, seldom more than 0.2 cc., however. This is somewhat large in comparison with the usual adult dose, but harmful effects were not seen. Occasionally pallor of the face and extremities (from vasoconstriction) was noted, of but a few minutes' duration without other signs of toxicity. It is my impression that the relatively large dose is necessary for effective results. The infants varied somewhat in their reaction to epinephrine; for instance, one of 0 Kg. weight was relieved of its suffering with 0.16 cc. and became quite pale with 0.2 cc., while a 5.5-Kg. infant of about the same age required 0.2 cc. for results and showed pallor only with 0.3 cc. The relief is usually striking, is noted promptly, often within two minutes, just as it is in urticaria, and may persist for an hour or more, and not infrequently the patient falls into a restful sleep."

SPECIAL ANTIDOTAL MEASURES IN IVY POISONING.—The vesicles and hullaec should be punctured and drained and the parts then thoroughly washed with soap (generous lather) and water. In washing and rinsing it is important to bear in mind that the object is to get rid of the irritant, therefore the soaping and rinsing must be done in the direction away from the unaffected parts; i.e., wash from the elbows down toward the hands and rinse in the same way. If the area is then rinsed or wiped over with alcohol, which is a solvent for the poison, this too must be done in the direction away from the unaffected skin. Gasoline also is a solvent to be used in the same way.

Lead.—Lead preparations, such as the lead and opium wash of the N.F. (lead acetate, 17.5 Gm., tincture of opium, 35 cc., water to make 1000 cc.), are not so popular now as formerly; at best they merely precipitate the poison, which must then be washed away.

Sodium Sulfite and Phenol.—Sutton says that a saturated solution of sodium sulfite, to which 0.5 per cent phenol has been added, has served him well; the following should be written:

Exsiccated sodium sulfite (U.S.P. IX).....	3viij	250.0
Phenol.....	3j gr. xv	5.0
Water to make.....	Oij	1000.0

Formaldehyde and Phenol.—Hessler has satisfactorily used formaldehyde and phenol; he writes: "My usual formula is: solution of formaldehyde (formalin), 5 cc.; saturated aqueous solution of phenol (1 : 15), 10 cc.;

distilled water to make 100 cc (to this may be added a drop of methylene blue solution, as blue is a color that leads people to pause about using internally To disguise the phenol odor, to which some object, a drop of some essential oil may be added) In dispensing I supply a 4-drachm vial with a swab in the cork and with the directions Apply freely the first time, after that use sparingly every few hours as needed The hardening and tanning effect of formaldehyde must be considered and explained to patients The earlier the solution is applied, the better the effect "

Zinc Sulfate—Irving writes enthusiastically of the use of zinc sulfate "All irritation and even eruption can be prevented if it is used immediately after exposure If used within twenty four hours after exposure or ten hours after the appearance of the vesicles, it will abort the attack If the case is not seen until the deeper layers of the epidermis are involved the cure is slower but just as sure To abort an attack, use 10 grains (0.6 Gm) of zinc sulfate to 1 ounce (30 cc) of water For later treatment, use half strength "

Ferric Chloride and Paraffin—McNair championed ferric chloride and paraffin "The effect of ivy poisoning is much like that of a burn and the treatment suggested resembles that used successfully during the war in burn cases The affected parts are first bathed with ferric chloride solution, to neutralize the poison The skin is dried and melted paraffin is painted over it A thin sheet of cotton is laid over the wound, and this also is covered with paraffin The affected area is thus protected from air and from rubbing, and new skin is given a chance to grow " The paraffin may also be swabbed on, as is often done upon the face This treatment has periods of popularity, but one should not overlook Traub and Teoneo's (1936) report of 2 cases of permanent pigmentation caused by it, Reyner (1939) also reported such a case which, however, was said to have responded to ultraviolet irradiation

Benzoyl Peroxide—Lamson (1931) stated that very great relief follows upon the application to the lesions of benzoyl peroxide as a dusting powder in a considerable proportion of cases, but pointed out the inadvisability of using the substance in this form because of its high inflammability and explosiveness A paste made from the powder and a lubricating jelly containing glycerin is said by him to be just about as effective and to be non explosive and no more inflammable than a bandage

Tannic Acid—Schwartz and Warren (1941) have reported the successful use of this agent in a small number of cases vesicles are clipped open with sterile scissors, or the smaller ones rubbed open with alcohol saturated gauze, and a dressing soaked in 10 per cent tannic acid solution applied for one half hour once daily

Collodion—Woodward (1940) reports that painting collodion over the affected sites brings instantaneous relief

Sodium Perborate "Protective" Ointment—Schwartz *et al* (1940) have reported that application of the following ointment affords protection to those exposed to poison ivy probably as a result of the detoxifying action upon the ivy oleoresin of the liberated oxygen, stearic acid (triple pressed) 200 Gm, potassium hydroxide (sticks) 14 Gm, alcohol (90 per cent) 40 cc, water 800 cc In Shelmire's (1941) hands this ointment has been no more protective than calamine or zinc oxide in vanishing cream, zinc oxide ointment or plain petrolatum, all of which offer only slight mechanical protection

Whole Blood Injections—Grimes (1931) reported a series of 20 cases in

which 10 cc of the patient's own blood was drawn from a vein and immediately reinjected into the gluteal region, the symptoms disappeared so rapidly that he suggested some sort of specific action. I have seen no further report of the use of this method.

Subacute Stage—After the more acute symptoms have subsided, the use of creamy pastes and salves may be begun, either for protection from clothing and dirt in the milder cases, or to tide over the period of subsiding inflammation in those cases in which it is apparent that the use of stronger stimulating and keratolytic agents will be later necessary. They are spread over the lesions like butter. Unna's soft zinc paste is much used.

Zinc oxide	3j	30 0
Precipitated calcium carbonate	3j	30 0
Linseed oil	3j	30 0
Solution of calcium hydroxide	3j	30 0

Lassar's zinc paste has a small amount of salicylic acid (2 per cent), which is slightly stimulating, and it is of such consistency that, if hydrous wool fat is substituted for half the petrolatum, a liberal dusting with talcum powder will form a crust on top of the application that requires little further protection from the clothing.

Salicylic acid	gr xl	2 5
Zinc oxide	3j	30 0
Starch	3j	30 0
Petrolatum	3ij	60 0

Another well known paste is that of Boeck.

Glycerin	5ij	12 0
Starch	5vj	24 0
Talcum	5vj	24 0
Solution of lead subacetate to make	3iv	120 0

Some observers of large experience like to use ichthyol in this stage, Becker (1931) favors the following.

Ichthyol (sulfonated bitumen N.F.)	3j	4 0
Zinc oxide	3j	30 0
Petrolatum to make	3iv	120 0

In using any of these pastes or salves, water should not be employed for their removal, use sweet oil, or the method of Glaze (described in the beginning of the section on local treatment).

Chronic Stage—Before applying any of the stimulating and keratolytic agents in effective strength, it is good practice to try out the sensitiveness of the skin with a very mild stimulant, for instance, the ichthyol zinc paste above, or one can proceed to the use of salicylic acid and the tars by first applying the following, in which each of the active ingredients is present only to the extent of 0.5 per cent (therefore, doubling these two figures would give 1 per cent, tripling 1.5 per cent, quadrupling 2 per cent, etc.)

Salicylic acid	gr iiss	0 15
Pine tar	gr iiss	0 15
Zinc oxide	3j	8 00
Petrolatum to make	3j	30 00

The best of the available tar preparations are pine tar, coal tar and oil of cade. For any of them, dosage must be determined in each individual case, as previously stated, the coal tar is often surprisingly well borne in high concentration. The oil of cade, which is prepared from juniper wood, has perhaps the least unpleasant odor, but all of the tars are nasty messes. The prescription containing tar a few pages back is a satisfactory basic one for coal tar therapy, or any of the tars may be combined with salicylic acid, as in the prescription just given. Perhaps it is of some value to know that the wood tars are acid in reaction and coal tar alkaline.

Sulfur may also be used in any proportion if the patient's tolerance is first carefully tested, the seborrheic greasy type will bear it best and derive the most benefit from it. In the following, 3 per cent is combined with 1 per cent of salicylic acid and an ointment instead of paste base is used.

Precipitated sulfur	5ss	2 0
Salicylic acid	gr x	0 6
White wax	3j	4 0
Hydrous wool fat	3v	20 0
Petrolatum to make	3ij	60 0

If greater, ocreate like consistency is desired, paraffin may replace the wool fat and be increased up to 50 per cent.

Resorcinol concentration must also be gauged by each patient's individual reaction, it is best perhaps to begin with 1 or 2 per cent, but less than 5 per cent is rarely effective on thickened areas, it is occasionally carried up to 20 per cent. The formula contains 5 per cent.

Resorcinol	gr xlv	3 0
White wax	3j	4 0
Hydrous wool fat	3v	20 0
Petrolatum to make	3ij	60 0

For more prolonged application, the paste base would be substituted.

Ammoniated mercury is also very useful at times, in the following, 5 per cent is combined with 20 per cent of the liquid tar preparation of the N.F.

Ammoniated mercury	gr xlv	3 0
Solution of coal tar	3 ij	12 0
Hydrous wool fat	3j	30 0
Petrolatum to make	3ij	60 0

There is twice as much wool fat as petrolatum here because of the necessity to incorporate the large amount of fluid, the anhydrous fat would be even better.

Local treatment of some sort is necessary in practically all cases of eczema-dermatitis, but it is by no means certain that in a given case the same preparation will be serviceable for all lesions. At times acute weeping areas on one portion of the body will demand wet dressings while lichenified areas elsewhere are being treated with the tars, salicylic acid, etc. Utmost cooperation on the part of the patient is of prime importance.

BOILS

(Furunculosis)

Boils are acute, deep seated, circumscribed inflammations of sebaceous glands or hair follicles, the causative organism is probably a staphylococcus in most instances. In the beginning the skin is smooth, tense and red, but in a few days the head of the elevation either becomes pustular or the whole mass becomes boggy, at this point the bod either discharges its pus and necrotic tissue or retrogresses without rupture. There may be a great many boils present at one time on various portions of the body surface, and in some cases new "crops" continue to appear for many months. The individual lesions are very painful and the patient is extremely uncomfortable, but the malady is seldom dangerous to life except in the diabetic or nephritic, or if the boils are on the face or upper lip. Of course, a crop of boils superimposed upon an acute infectious disease is a very serious matter.

THERAPY

General Measures—The individual suffering from this affliction should be given a complete physical examination, during which the discovery of some debilitating constitutional disease may furnish the key to the therapy. The elimination of demonstrable foci of infection has sometimes been followed by rapid improvement, but by no means regularly. "Specific" immunization with stock or autogenous vaccines has been going on for a long time now and has as yet very little to its credit. Bacteriophage has almost completely failed here as in most other diseases.

The drugs used internally in the attempt to put a stop to the attack are legion, which probably means that none of them are consistently of value. I therefore set down here only those prescriptions that I believe to be most often employed—as to the rationale of their use, perhaps the least said the better.

Rumex mixture

R ^j Potassium acetate	℥vj	24 0
Tincture nux vomica	℥ij	8 0
Fluidextract of rumex to make	℥iv	120 0
Label 1 teaspoonful after meals		

or

Startin's mixture

R ^j Ferrous sulfate	℥j	4 0
Dilute sulfuric acid (U.S.P.)	℥iv	15 0
Magnesium sulfate	℥j	20 0
Syrup of ginger	℥j	30 0
Water to make	℥iv	120 0
Label 1 teaspoonful after meals and upon retiring or 4 teaspoonfuls before breakfast		

or

R ^j Dilute sulfuric acid (U.S.P.)	℥viij	90 0
Label 20 drops in water after meals		

or

R ^j Calcium sulfide	gr viij	0 4
Lactose sufficient to make 24 capsules		
Label 1 capsule after meals and upon retiring		

Ewell (1935) reports that intravenous injections of neoparsphenamine at five-day intervals have served himself and associates very well. There are of course reports of the successful employment of the sulfonamides, particularly sulfathiazole, but I should certainly like to see a good account of a thoroughly controlled study before stating that this new drug has solved the riddle of the ancient affliction of Job.

Irradiation—There are many enthusiastic reports of the results of x-ray therapy, but I like always to remember what sanguine and optimistic fellows the roentgenologists are. Still, Fink (1941), of the University of Minnesota Hospitals, recently reports that 25 of 30 treated patients were definitely and quickly relieved, and that is of course something. Ultra short wave diathermy was having a great vogue a few years ago, it seems to me one does not hear it mentioned in this connection quite so often nowadays.

Local Treatment—I do not believe that there is any known substance that will abort the lesion when applied locally, the heavy application of full strength tincture of iodine while the furuncle is still small probably has the best reputation. To hasten its maturation, in order that the contents may be evacuated spontaneously or with the aid of the knife, hot compresses are sometimes of value, though it is often very difficult to accelerate the pace of a boil's development. Certainly linseed or any other kind of special poultice (honey, sugar, bacon, bread and milk, or the whatnots of household medicine) has an advantage over the plain water beyond the requiring of less attention after it is applied, but the addition of an antiseptic, such as 1 teaspoonful of compound cresol solution to the pint of water, is of value in protecting the surrounding skin. To make a linseed poultice, add 1 part linseed meal with constant stirring to about 3 parts of boiling water to make a thin dough, spread about $\frac{1}{2}$ inch thick on cloth and fold the edges to prevent escape, cover with oiled silk and cotton after applying. The poultice may be reheated as often as needed.

The body should be kept absolutely clean by a daily bath with hot water and soap, 4 ounces (120 Gm) of boric acid may be added to the small tub of water. It is well after the bath to pat the body dry with a clean towel rather than to rub it, a procedure that will lessen the liability of the infection to spread by contact, and also protect any small pimples that might be present from abrasion and consequent greater liability to infection. Underclothing and bedclothing should be changed daily.

Incision—It is usual practice to freeze the skin over the boil with ethyl chloride before incising, but all of us know that the resulting anesthesia is far from satisfactory. Mabry (1937) has evolved the following improvement in technic as a result of having been himself afflicted with a series of boils. 'The furuncle is frozen as has always been done. A towel clamp now grasps the frozen skin and lifts it up or away from the body while the knife makes pressure inward. The inward pressure of the knife becomes a balancing or counteractive force against the towel hook. This prevents the deep pressure being made over the hard, inflamed hypersensitive mass and eliminates the pain, because the pain has always been caused by the knife pressure on the indurated mass and not by the cutting.'

ACNE

Acne is an inflammatory skin disease symmetrically involving the face, sometimes, also, the interscapular or sternal regions are involved, and occasionally the whole back. The skin is greasy, contains many blackheads (comedones), and the acne lesions, which are at first papular, then become pustular, and finally dry up with more or less crusting. The essential process in the disease is a functional overactivity of the sebaceous glands, combined with a follicular hyperkeratosis, upon this is superimposed pustulation, and, at times deep seated granulomatous infiltration. Neither the so-called "acne bacillus" nor any other organism is any longer believed to be of primary etiologic importance. Acne being essentially a disease of adolescence, there is every reason for suspecting that an endocrine imbalance lies at the root of the matter, but proof of the fact is not yet at hand. The first appearance of the disease in an individual past twenty five should cause the physician to inquire into the occupation (tar, oils, paraffin, chlorine), search for foci of infection, and question regarding the use of goiter preventives.

The consensus is that the ingestion of iodine, even in the small amounts contained in iodized table salt, causes an increase in the number and severity of the lesions, but there are a few men of experience who disagree with this opinion. It is said that acne is of rare occurrence among such primitive peoples as the Eskimos, native black Africans, Austrahan aborigines and Maoris, but that as these people adopt modern methods of living the condition occurs more frequently.

THERAPY

General Measures—The acne patient should be given a thorough physical examination, and especially should a careful history of past ailments be taken, for the elimination of chronic foci of infection has occasionally been rewarded by rapid improvement. Usually, however, the malady responds all too slowly to any type of treatment. Here, as everywhere else, I am opposed to the routine employment of drugs "to keep the bowels open" unless constipation is actually shown to exist—and even then cathartics are rarely indicated (see Colon Consciousness). Startin's mixture is used in nearly every case at some time, very likely it has no more value than accrues from giving the patient something to take from a bottle.

Startin's mixture

R Ferrous sulfate	℥j	4 0
Dilute sulfuric acid (U.S.P.)	℥iv	15 0
Magnesium sulfate	℥j	30 0
Syrup of ginger	℥j	30 0
Water to make	℥iv	120 0

Label 1 teaspoonful after meals and upon retiring, or 4 teaspoonfuls before breakfast

There is certainly less belief today than there was a few years ago in the excessive use of carbohydrates, especially "sweets," as important in prolonging the siege. Crawford and Swartz (1936), who deliberately maintained patients on a high carbohydrate regimen, failed to find the diet in the least harmful. Wortis (1937) reported great improvement of the acne in 6 patients undergoing hypoglycemic insulin treatment of psychoses. Semon and Herrmann (1940) also reported improvement in all of their 13 patients in

whom insulin was used primarily to combat acne, but let us go slowly here for insulin is not an agent to play with lightly and certainly much harm would be done if word began to go around about the "insulin cure for acne." Cormin (1940) was able to detect clinical evidence of food sensitivity in 20 per cent of his 32 patients, 70 per cent of whom were helped by food eliminations. The allergic approach, especially from the standpoint of food allergy, may perhaps be well rewarded once in a long while. There is no evidence as yet showing any of the endocrine products to be of proved worth, though that is certainly at present the most tempting avenue for investigation. Viosterol has now had a number of years' trial and still does not have any very impressive list of consistent successes to its credit. What has been said of vaccine therapy in furunculosis will apply equally well here in acne. Yeast should certainly be left to the quacks.

Local Treatment—The things necessary are to get rid of the blackheads, cleanse and disinfect the skin as much as possible, and apply a keratolytic agent. The face should be bathed in hot water until it becomes quite red, the blackheads pinched out, or preferably removed with an extractor, all abscesses incised and drained, the face again bathed in hot water to which 1 teaspoonful of the compound solution of cresol has been added to the pint and then the keratolytic should be applied. At the New York Skin and Cancer Hospital it was formerly, and probably still is, despite the fancy new name for the hospital, the custom to write for *lotio alba* in strengths designated as 2 ply "4 ply" and "6 ply." The formula below is for the 2 ply lotion, the 4 and 6 ply were obtained by keeping the total quantity of the lotion constant but doubling and trebling the 2 active ingredients.

Zinc sulfate	3ij	8 0
Sulfurated potassa	3ij	8 0
Water to make	3iv	120 0

This is to be applied at night and washed off in the morning with hot water and some such gritty soap as hand sapofo, it has also been recommended that potassium nitrate be added to the water in the proportions of 30 grains (2 Gm) to the pint (500 cc). After drying, talcum powder to which has been added 1 drachm (4 Gm) of sulfur to the ounce (30 cc), should be freely dusted on. This treatment, because of its violence, has frequently to be interrupted by periods during which only cold cream is used at night and calamine lotion during the day.

Karp *et al* (1939) reported great improvement in nearly all of the 50 patients whom they treated by the application of slush therapy, which they called "cryotherapy" the application of a mixture, which forms a slush, of carbon dioxide snow, acetone and sulfur. Dohes and Keil (1940), using the method in 115 patients, did not obtain nearly so good results and reported several unpleasant reactions and a number of contraindications, decidedly it seems to me this treatment should be left to dermatologists to study and not be employed by others as yet.

Ultraviolet Light—This agent is highly capricious in its effectiveness, just as is natural sunlight. It always seemed to me that the only cases deriving more than a superficial specious benefit from its use were those in which considerable peeling of the skin was induced, but its success even in cases burned to this extent was far from predictable in my day. Dermatolo

gists tell me that its status has not changed in the years since I have had any intimate experience with it

Other Measures—I think there can be no better guide for the general practitioner than a résumé of the opinions of the following outstanding dermatologists published in a symposium on acne in the *Journal of Investigative Dermatology* in mid-1940 Joseph V Klauder, George M Mackee, Henry E Michelson, Hiram E Miller, Richard L Sutton Sr, Udo S Wile. All agreed that endocrine therapy is without value, vitamins were considered useful only to improve the general health. Five of the six found vaccines and toxoids without value. Anemia was considered to be casually and not causally associated with acne and the administration of hematinics was held of little if any value. Roentgen therapy was regarded as of some but not dominant value in treatment; one of the group resorted to it in about 25 per cent of his cases, one restricted it to patients above fifteen years, another above sixteen, another above seventeen, all were more or less opposed to repetition of a single course. Roentgen therapy was felt to be most effective when combined with other measures. Four of the group stressed the importance of extracting comedones and opening pustules; one did not do this and one felt that it might aggravate the condition. The importance of local medical treatment was agreed to by all the group.

WARTS

Warts, as is well known, are seen principally in children, but they may develop for the first time in adults. The most frequently encountered types are the small flat, so-called 'juvenile' warts occurring principally on the face and backs of the hands, the larger excrescences, known as verruca vulgaris with a predilection for the backs of the hands and wrists, but also occurring on all other parts of the body, the plantar wart of the sole, and the projecting filiform, narrow based type, seen principally on the face and scalp. It is now believed that warts are caused by a filtrable virus, they seem to be auto inoculable.

THERAPY

Local Treatment—Perhaps the most valuable method employed at the present time is fulguration, the lesions turn black and drop off several days after treatment. The use of x rays is often enthusiastically lauded, and recently radium also, doubtless the results are excellent in most cases, but it seems to me that warts are very benign affairs in which to use these potent and dangerous agents, certainly only skilled dermatologic radiologists should be permitted to give such treatments. For the treatment of single lesions in which temporary unsightliness and a certain amount of scarring are not objected to the use of ethyl chloride, the curet, and silver nitrate are quite effective. The site is frozen with the ethyl chloride (which in itself is said to be effective in destroying warts) the lesion is quickly curetted out, and the wound is then thoroughly treated with the silver nitrate stick. Carbon dioxide snow is often effectively used. The following are examples of the

great variety of caustics and keratolytics that are applied, they sometimes succeed in accomplishing the removal of the lesions, but the process is usually very tedious

Salicylic acid

R	Salicylic acid	℥iss	6 0
	Collodion	℥j	30 0
	Label Touch the wart two or three times daily with the solution, having previously removed the adherent collodion		
R	Salicylic acid	℥iss	6 0
	Chloral hydrate	℥iiss	10 0
	Collodion	℥j	30 0
	Label As above		
R	Salicylic acid	℥iss	6 0
	Mercurous chloride	gr xv	1 0
	Hydrous wool fat	℥v	20 0
	Label Apply to wart several times daily		

Arsenic—This drug is usually applied in the form of Fowler's solution (U S P solution of potassium arsenite), first softening the lesions by the use of a 5 per cent solution of potassium hydroxide. A modified Marsden paste (Hare) may also be applied if the warts are few

Arsenic trioxide	gr lxxv	5 0
Acacia	gr lxxv	5 0
Cocaine hydrochloride	gr xiv	2 0
Glycerin	℥xxx	2 0
Water to make a paste		

This is applied on gauze and kept in place for twenty four to thirty six hours, the slough is then poulticed away. This is radical treatment.

Strong Acids—Chromic "acid" is applied in 20 per cent solution. Nitric acid is applied full strength with a glass rod and neutralized with salt solution when it has corroded deeply enough. Trichloroacetic acid is applied in liquid form with a glass rod.

Vlemminckx's Solution—This, the solution of sulfurated lime of the N F, is made as follows: mix 165 Gm of calcium oxide with 250 Gm of sublimed sulfur and add gradually to 1750 cc of boiling water, boil, with frequent stirring, to 1000 cc and maintain this volume by additions of water while boiling for one hour, cool, strain, and decant the clear brownish liquid after standing. Pusey writes that "the solution has served me well in many of these troublesome cases. The method of application that I have found most effective is to put on a small dressing just a little larger than the wart, wet with full strength Vlemminckx's solution and held in place by adhesive plaster. This is left on over night and repeated until irritation is produced, then it is used less frequently until the wart disappears, or until, in case of plantar warts the desiccated horny mass can be dug out."

Urea—MacKay (1940) has found the injection at the base of the wart of 0.1 to 0.2 cc of 50 per cent urea solution to be useful in about half of a very small series of patients.

Irradiation—Oliver (1940) claims successful treatment of about 92 per cent of 49 patients given a single x ray exposure and of about 80 per cent given a single radium exposure. Marks and Franseen (1940) take the conservative view that many such good results are based on follow up examinations made before the late end results could be known, they counsel that a second treatment should be given only with the greatest circumspection if massive dosage has been used no matter how long the interval.

Systemic Treatment—All of the antisypilitic drugs—mercury, the arsphenamines, bismuth—have been used much as in the treatment of the major disease. Nitrohydrochloric acid, employed as in bay fever, also has had a trial. Response to any of these drugs is extremely variable most of the successes apparently being had in cases of warts of the flat "juvenile" type.

Treatment by Suggestion.—In Kentucky, in my childhood, the method was to rub the cut side of a potato on the wart, bury the potato and wait, I do not recall the results. A bit further west in the land of Tom Sawyer, there was something about a bloody barn and a cat in the graveyard at midnight, if memory serves me correctly. The practice in Timbuctoo is not known to me. In Zürich some years ago, Bloch risked his reputation by asserting his belief that warts could be cured by suggestion, Sulzberger (1934), who studied under Bloch has recently stated that he also uses *bocus pocus* effectively at times, and others have reported in the same vein. I wonder if this advances us very much?

HERPES ZOSTER

(*Shingles*)

Herpes zoster is an acute inflammatory skin disease characterized by the appearance of crops of vesicles seated upon erythematous bases along the course of one or more of the peripheral sensory nerves, the sites of predilection being the thoracic, lumbar, brachial and supra-orbital regions. In the average case the lesions dry into crusts and disappear in a week or two with little or no accompanying pain, but in severe cases there may be many successive crops of vesicles that persist for a long time and become pustular rarely even gangrenous, pain of neuralgic character is usually severe in these cases, and in the elderly there is often much pain though the eruption be slight. The disease is now generally conceded to be a specific neutro infection of the posterior root, gasserian or geniculate ganglia or paraganthionic tissues, with secondary manifestations in the skin. A few observers, however, maintain that herpes is an atypical form of chickenpox, but the evidence so far brought forward in favor of such a view is of very doubtful value. Gais and Abrahamson (1939) have stressed the difficulty of differentiating herpes before the eruption from certain intrathoracic and intra-abdominal lesions.

THERAPY

The eruption runs a self limited course that apparently cannot be modified by treatment. Indeed, in most cases the only indication is to protect the lesions from traumatism and subsequent infection. For this purpose it usually suffices to apply a dusting powder of thymol iodide and cover the parts with cotton held in place by adhesive strips. For the relief of moderate pain the usual analgesics are used. In severe cases the pain is not so easily relieved, resort to the opiates can of course be had, but codeine sometimes does not suffice and the objections to the prolonged use of morphine or dilaudid are obvious. Of the many local applications devised for the relief of this pain, only two are, I believe, of relatively uniform value, the occasional spraying of the skin over the affected ganglion with ethyl chloride, and the application of paraffin or of collodion. Siddick (1930) has reported very successfully upon the use of injections of pituitrin, as suggested some years ago by Vandel. Fifty four patients were given injections intramuscularly of 0.5 to 1 cc. at twenty four hour intervals, most of them required only 2 injections but a number required 3 and one as many as 6. He found pregnancy the only contraindication to the treatment and occasional momentary faintness the only untoward effect. Niles (1932), Gillett (1934), and Lewsen (1934), have also reported favorably. Ruggles (1931) had excellent results in 15 cases from the intravenous administration of sodium iodide, routinely he employed a 20-cc. solution of 30 grains (2 Gm.) on the first, second, fourth and seventh days, but several of the patients did not require the full course. Phillips and Morginson (1932) and Beers (1939) also used the iodide injections successfully. Secunda *et al.* (1941) have infiltrated the areas of hyperesthesia with 0.5 to 2.0 per cent procaine solution with relief of one to thirty hours' duration in a small series of cases. Rosenak (1938) injects procaine solution into the intervertebral and prevertebral ganglia, which is certainly a much more difficult procedure, however, he reports that pain ceased and the vesicles dried within twenty four to forty-eight hours in 20 of 22 patients so treated. Walker and Walker (1938) reported that they have obtained relief from pain in cases involving the eyes and forehead and side of the nose by injecting 5000 units of diphtheria antitoxin, I cannot imagine how one would justify such treatment on rational grounds, but this is true of other types of treatment as well. Both Sutton and Stelwagon state that a mild galvanic current (1-5 mm.) is often of very great service in persistent neuralgias. The positive electrode is placed over the affected ganglion, the negative drawn along the course of the nerve backward toward the cord, it is recommended that the current be used during ten or fifteen minutes each day. Paravertebral alcohol injections are sometimes necessary. There have been a number of reports of the successful employment of x ray therapy over the spinal root ganglia of the nerves involved—for example, McCombs *et al.* (1940) felt that they were successful in checking the pain in 39 of the 41 patients who began treatment within the first seven days of the course of the disease, but I must add that there are many men who are wholly skeptical of the value of roentgen therapy in this malady. It has been reported that thiamine hydrochloride (vitamin B₁) therapy is helpful in herpes zoster, but Rattner and Roll (1939) did not find it to be so in the 16 cases in which they tried it.

PRURITUS ANI

There are many ascertainable causes for itching about the anal region such as constipation, colitis, cirrhosis, carcinoma, anal fissure, hemorrhoids, pinworm infestation, bacterial or mycotic infections, diabetes mellitus etc. Removal of the cause will bring complete relief in many instances, but there also exists a class of cases to which the word "idiopathic" can be correctly applied since they are associated with no demonstrable etiologic factors and respond but poorly to the milder types of treatment. Very interestingly, however, Foster and Hill (1940) have drawn attention to the frequency with which attacks of pruritus ani occur in association with exacerbations of seborrheic dermatitis of the scalp, ear canals, eyelids, umbilicus or axillas or of dermatophytosis of the feet.

Local Antipruritic Measures—Absolute cleanliness is essential, the parts being washed after every defecation. Oftentimes the application of a hot wet pack for a few minutes after washing brings relief which persists for a half hour or more. The following are examples of the antipruritic ointments that are most frequently used.

Yellow mercuric oxide	gr xx	12
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Ammoniated mercury	gr xl	24
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Crude coal tar	℥ij	12.0
Zinc oxide	℥ij	12.0
Petrolatum to make	℥iv	120.0

The amount of coal tar contained here, 10 per cent, may be much increased.

Phenol	gr xl	24
Zinc oxide	℥ij	12.0
Ointment of rose water (U.S.P.) to make	℥iv	120.0
Phenol	grxx-xl	12-24
Menthol	gr xx-xl	12-24
Ammoniated mercury ointment (U.S.P.)	℥j	50.0
Zinc oxide	℥j	50.0
Anhydrous wool fat	℥ij	60.0
Lime water to saturate and make ointment		
Ethyl aminobenzoate (benzocaine)	℥ij	12.0
Salicylic acid	gr xlv	30
Hydrous wool fat to make	℥iv	120.0
Benzyl alcohol	℥iss	60
Hydrous wool fat to make	℥ij	60.0

Injection Therapy—Since 1916, when Stone introduced perianal injection methods, many solutions have been used with varying success. Nicobol in 95 or 40 per cent strength, dilute hydrochloric acid, phenol, etc. Gabriel's formula, introduced by him in 1930, has won many advocates since it contains an anesthetic, nupercaine, phenol, which apparently intensifies the

anesthetic action, and alcohol, which destroys the nerve filaments. The proportionate constituents are, nupercaine, 0.5 per cent, benzyl alcohol, 10 per cent, and phenol, 1 per cent in sterilized sweet almond oil. With this mixture it is said that anesthesia generally persists for two to six weeks, there is no pain in the injection itself except the first prick of the needle, very little likelihood of sloughing occurring, no systemic reactions, and a procedure simple enough that it can be employed in the office. In 1936, Steinberg reported that in a series of 100 patients followed over a period of two years or longer, in 51 per cent the results were excellent, and satisfactory in 78 per cent, in all instances temporary relief of at least one month was obtained. Steinberg's technic follows:

"The perianal skin is cleansed with tincture of green soap and painted with Scott's solution (mercuochrome crystals 2 parts, distilled water 30 parts, acetone 10 parts, and alcohol 55 parts) or tincture of merthiolate (1:1000). One ampule of nupercaine phenol benzyl alcohol in oil, which has been slightly warmed to facilitate the flow of oil, is drawn into a 5 cc. sterile glass syringe through a large caliber needle. The needle is then changed to one of gauge No. 21, $1\frac{1}{2}$ to 2 inches long. The perianal region is then divided into four quadrants, and usually either the left or right posterior quadrant is chosen first. The patient should lie in the Sims' position on the side selected for the treatment. The needle is inserted subcutaneously about one half inch outside the affected area. *It must be freely movable at all times.* The solution is then injected in fan shape manner until all the 5 cc. have been used. *The injected tissues are massaged gently for about 3 minutes* with a sterile piece of gauze, thus assuring an even distribution of the oily solution. The second injection is given 2 days later in the opposite posterior quadrant, and at 2 day intervals, the two anterior quadrants are treated in a like manner. *Great care should be taken not to inject the solution too superficially or intradermally, as sloughing will invariably follow.* The external sphincter muscle should not be injected because if more than one quadrant of the muscle has been injected, the anal canal may become patulous and temporary loss of control take place."

Tattooing—Just about the latest of the thousand and one treatments advocated for control of pruritus ani is the tattooing of the region with mercury sulfide. Turell (1940), who is apparently the chief student of the subject, reports good results in the cases refractory to other more usual types of treatment in which he has resorted to this measure, but the matter is still experimental and certainly not yet ready for application by the general practitioner.

Surgery—Surgeons are performing perianal subcutaneous neurotomy which they say is effective in stopping the itching, I do not know the criteria upon which cases are chosen for this procedure.

X-ray—This agent in the hands of a properly qualified expert will by no means relieve every case but it does have some brilliant successes to its credit. Upon the other hand, the relief it affords is seldom permanent and many men feel that the pruritus which returns after a period in which it had been held in temporary abeyance as a result of the treatments is far worse than that originally treated.

SCABIES

Scabies is an infectious disease caused by an animal parasite, *Acarus scabiei*, the female of which incites the itching by burrowing into the skin in order to lay her eggs. These burrows, which are tortuous and marked by a slight elevation at one end and a grayish speck at the other, can be seen with a strong hand lens. The sites of predilection are the dorsal surfaces of the webs between the fingers, the anterior axillary fold, the lower abdomen, the nipple region in the female, and the shaft of the penis in the male. In cleanly individuals the spread is usually not beyond these points, but in dirty individuals and in severe cases the whole body may be involved, though the face and scalp nearly always escape. In children the palms and soles are also often infested, superimposed eczematous and impetiginous lesions are also frequent in young patients and in patients of any age who do not resist the desire to scratch excessively. The disease probably never disappears spontaneously. In England since the blitzkrieg of 1940-41 scabies is said to have become a veritable scourge due to crowding in the shelters and the wide scattering of evacuees throughout the country. As long ago as 1687, Bonomo showed that the malady is associated with the presence of *A. scabiei*, indeed this is the first infectious disease to have its etiology established.

THERAPY

Sulfur—*The older method* of using sulfur to combat scabies is to make an ointment of 20 per cent sulfur, 30 per cent soft soap (or up to 20 per cent potassium carbonate) to facilitate access to the parasites by softening. Fantus (1930) advocated the use of the following formula, in which there is 10 per cent oil of cade, for antipruritic effect:

Oil of cade	5ij	12 0
Precipitated sulfur	3vj	24 0
Soft soap	3jssj	36 0
Petrolatum	3iss	48 0

The patient must first take a soaking bath, followed by brisk toweling, then rub the ointment into the body, except the face and scalp, powder with talcum if desired, and go to bed. Repeat on each of three to five nights, removing the ointment if necessary during the day. Stokes (1936) has ointment applied on the first night, next morning, and again that night, the bath is taken on the second morning. Fresh underwear should then be put on and the bedclothes sent to the laundry and the suit ordinarily worn should be sent to the cleaner. All members of the family must be treated. Some men use only one fourth to one half the amount of sulfur for children. Soothing ointments and baths will easily control sulfur dermatitis should it appear.

The "Danish" method of using sulfur is thought by many to be superior, but the opinion is not unanimous, quicker it certainly is, but some men claim it is less effective than the slower method and more likely to be followed by dermatitis. The patient merely applies the ointment after a preliminary bath and drying, goes to bed for twenty four hours, and then removes the ointment, with bath and disinfecting measures following as in the older method. I quote Greenwood's description of the ointment, as prepared for him at the Massachusetts General Hospital (cure in 93.8 per cent

of 4522 cases, dermatitis in 5.6 per cent—Greenwood and Reilly, 1937) It should be distinctly understood that to have this ointment used on successive days is to invite dermatitis of a severe order

"One Kg. of sublimed sulphur is mixed with 2 Kg. of 50 per cent solution of potassium hydroxide (as free from water as can be obtained) Gentle heat is applied until reaction ceases and the solution becomes clear When the process is complete, one should be sure that the sulphur is in excess to a slight degree

"Petrolatum, 225 Gm., is mixed with wool fat, 225 Gm., without heat

"To this mixture is added 375 Gm. of the solution of sulphur and potash mentioned above

"To 40 Gm. of 20 per cent sodium hydroxide solution is added 28 Gm. of zinc sulphate The mixture is agitated thoroughly until reaction ceases, poured on filter paper, and washed thoroughly, then the washed precipitate is added to the foregoing

"Liquid petrolatum is added to obtain a total weight of 1000 Gm

"Five Gm. of oil of bitter almond is added to check the somewhat disagreeable odor of hydrogen sulphide"

This ointment is now available in proprietary form as Tilden's Danish Scabies Ointment and also as Scabicide of the Upjohn Co

The lather tablet method, introduced by Carter (1941) in England, employs a tablet containing 12 grains (0.72 Gm.) of sulfur incorporated with a lathering agent, the advantage being that the overzealous cannot apply too much sulfur when employing it in this form Three successive treatments are given as follows (a) hot, scrubbing bath, (b) rub up the tablet between the wet hands and apply the lather all over the body, (c) put on the underwear after the lather has been allowed to dry on the body

Benzyl Benzoate—Kissmeyer, in 1937, described a rapid treatment method employing a formula consisting of equal parts of soft soap, isopropyl alcohol, and benzyl benzoate The patient rubs soft soap over the body, soaks in a hot bath for ten minutes during which he rubs himself, and then rising out of the bath but while the body is still wet, lotion is applied all over the body with a stiff-bristle brush for five minutes The patient then rests until the body is dry, after which another application of the lotion is made and brushing resumed for another five minutes, after this the body is gently dried and the patient puts on again the clothes previously worn Twenty-four hours later a bath is taken and clean clothes put on It was said that at the Kommunehospital, Copenhagen, 8000 cases of scabies had been very effectively and cheaply treated in this way and without serious post therapeutic dermatitis

This treatment has been much used in England during the present epidemic and apparently with excellent results, isopropyl alcohol has been replaced by ordinary ethyl alcohol or denatured rubbing alcohol without lessening the efficacy of the treatment Warren (1940) writes that children under six years are likely to develop an erythema and that most outpatients require applications on two successive days, most men, however, seem to be getting results with only one treatment provided all intimate contacts can be treated also Ingels (1939), who treated a large number of cases in San Francisco, found that the lotion could be satisfactorily applied simply by rubbing it in briskly with the hands

Carter (1941), in England, records the practical observation that attendance at a clinic falls off when this benzyl benzoate treatment is used because the alcohol contained in the lotion causes severe burning pain when there are open sores or septic infection of the furrows. She says that in order to overcome this stinging effect the benzyl benzoate has recently been incorporated in a cream and satisfactorily used by others though she had not herself used the cream at the time of writing.

Sodium Thiosulfate.—Sheppard (1940) paints the whole body below the neck with a 40 per cent solution of sodium thiosulfate allows it to dry for fifteen minutes then paints a 5 per cent solution of hydrochloric acid over the thiosulfate and allows it to dry for fifteen minutes, then repeats the entire treatment after two hours. Fresh linen is then given and the whole procedure repeated on the next day, a bath being taken twelve hours after the second day's treatment. If further treatments are required an interval of three to five days is allowed to elapse, in children under seven years the strength of the solutions is cut in half. This is of course just a new form of sulfur therapy, but it has had wide employment in recent years, Dr. Sheppard has recently informed me that his favorable impression of the method continues after having applied it in hundreds of cases in India.

Rotenone or Derris Root.—Rotenone is an active principle obtained from derris root which has long been employed in flea powders. Thomas and Miller (1940) have prepared a lotion from rotenone as follows. Dissolve 1 Gm. of rotenone in 3 cc. of chloroform and add with vigorous shaking to a mucilage of quince seed and Irish moss (containing 0.1 per cent sodium benzoate as preservative) in sufficient amount to make a 1 or 2 per cent solution. The patient bathes at night, scrubbing and soaking well, dries and then rubs the lotion in all over the body except the face and scalp the next morning and evening and again the next morning the applications are repeated, on the evening of this last day the patient bathes thoroughly and changes underwear and bedding. Thomas and Miller obtained cure in all of their 24 cases without causing any irritation of the skin but some of the more severe cases required a second course of treatment with the 2 per cent lotion.

For application to armies in the field Saunders (1941) has employed derris root powder itself, stirring 4 ounces (120 Gm.) into 1 gallon of cold water and adding 1 teaspoonful of soap flakes to each half pint of the lotion as it is issued. The patient applies this all over the body from the neck down three times daily for two days without preliminary bath and without change of clothing. Saunders reports very satisfactory results. The method certainly has the merit of great simplicity but it is admitted to cause in some instances irritation of the scrotum and penis with perhaps excoriation and a slight transient serous exudation in a few cases.

• SCHISTOSOME DERMATITIS

(*Swimmer's Itch*)

(See chapter on Flukes)

HEAD LOUSE INFESTATION

Kerosene.—The ordinary grocer's kerosene is usually diluted with equal parts of olive or cottonseed oil to render it less inflammable; the scalp is then thoroughly soaked with this mixture and covered with a loose cloth. The head should be kept covered for twenty-four hours, after which the mixture is to be thoroughly washed out with soap and warm water. The treatment may be repeated as often as is necessary with intermissions of a few days.

This treatment is fairly effective in killing the lice, but it does not destroy most of the nits at the first application. The fine comb should be freely used between treatments.

Xylol.—The usual mixture used is equal parts of xylol, alcohol and ether; this is of course very inflammable but evaporates quickly. One thorough treatment of the scalp and hair with this preparation usually suffices to kill all the lice and nits, but the latter adhere more tightly to the hairs after being killed in this way than they do while alive. The fine comb must be diligently employed; it is said that vinegar will wash out the nits, but Buxton (1940) states that this positively is not so. The treatment can, of course, be repeated if necessary.

Mercuric Chloride.—The bichloride of mercury is used 1 500 in 50 per cent alcohol as follows:

R	Mercuric chloride (bichloride).	gr xv	1 0
	Alcohol.....	O. s	250 0
	Water to make .	Oj	500 0
	Label. Apply to hair and scalp as directed.		

The hair and scalp are thoroughly anointed with this solution twice daily for three or four days. This is a very clean method but if the scalp is abraded the alcohol is likely to cause considerable momentary smarting pain.

Larkspur.—This substance, which is delphinium of the N.F., is not so much employed nowadays as formerly, either of the three previously listed mixtures being superior to it in most instances. Of the many formulae for its preparation, the following is perhaps the cheapest and easiest compounded.

Larkspur seed ..	100 0
Potassium carbonate	10 0
Alcohol	500 0
Water to make.	1000 0

Mix the seed and the carbonate with 500 cc. of water, boil the mixture for five minutes; when it has become cold, add the alcohol, strain, and add enough water to make the finished product measure 1000 cc. Filter, if not clear. Larkspur is poisonous and if there are abrasions of the skin may be sufficiently absorbed to cause symptoms like those of excessive aconite action: tingling of mouth and skin, gastro-intestinal symptoms, restlessness, collapse.

BODY LOUSE INFESTATION

So far as the patient himself is concerned it is usually sufficient in civilian practice to have him take a good cleansing bath with soap and hot water, and later apply one of the mercuric chloride lotions used in the treatment of crab louse infestation, preferably the one without alcohol, which would likely be disagreeable for a few moments if there is severe excoriation. In some instances it may later be necessary to use some one of the soothing lotions or creams if scratching has excessively irritated the skin. The clothing and bed-clothing must then be disinfected by autoclaving at 130° F (50° C) for thirty minutes or 140° F (60° C) for fifteen minutes. Ironing the clothing and bedding with hot irons is at best only a makeshift method by no means reliable. Disinfecting fluids in which they may be placed for twenty to thirty minutes, if autoclaving is impracticable, are (a) gasoline, (b) cleaner's naphtha, (c) compound cresol solution, at a temperature above 32° F (0° C). A description of disinfestation methods as applied to people *en masse* is not within the province of this book. Buxton (1911) says that the British have developed a powder and a liquid insecticide which when applied to a garment will keep it louse free for a week and a month, respectively, for war reasons the formulae are being kept secret.

CRAB LOUSE INFESTATION

In addition to scrupulous cleanliness, accomplished by the frequent and vigorous employment of soap and water, the pubic region should be shaved and the hair on the abdomen, thighs, lower part of the back, chest, axillae, eyebrows and border of the scalp thoroughly searched for nits. Any of the following preparations will usually destroy crab lice if applied several times daily.

Mercuric chloride	gr iv	0 25
Alcohol	℥iv	120 0
Water to make	℥vi j	240 0
Mercuric chloride	gr iv	0 25
Diluted acetic acid	℥iij	12 0
Water to make	℥viij	240 0
Tincture of cocculus (N.F. V)	℥ij	60 0
Alcohol	℥ij	60 0
Water to make	℥vi j	180 0
Ammoniated mercury	℥iss	6 0
Hydrous wool fat	℥j	30 0
Petrolatum to make	℥ij	60 0
Ointment of yellow mercuric oxide (U.S.P.)	℥ij	60 0
Mild mercurial ointment (U.S.P.)	℥ij	60 0
Xylol	℥ss	15 0
Hydrous wool fat	℥j	30 0
Petrolatum to make	℥ij	60 0

ACUTE POISONING

ACUTE POISONING

THE CORROSIVE ACIDS AND ALKALIS

The corrosive acids and alkalis most frequently swallowed accidentally or with suicidal intent are sulfuric, nitric, hydrochloric and oxalic acids sodium or potassium hydroxide (lye), sodium or potassium carbonate, and ammonium hydroxide (household ammonia) The general symptoms of the group are corrosion of the mucous membranes from the lips down to the pylorus, extreme pain, soon followed by the vomiting of food, shreds of mucosa, mucus, and blood that is dark brown due to the conversion of hemoglobin into hematin and other products, profuse bowel movement that is at first normal but later contains blood and shreds of mucosa, respiratory symptoms due to contact of some of the corrosive material with the air passages, and quick shock and collapse Those escaping immediate death may succumb to perforation of the stomach or the symptoms resultant upon stricture of the esophagus or pylorus In addition, the takers of concentrated ammonia are subject to early unconsciousness and standstill of the heart, and those having swallowed oxalic acid (much used as a bleaching agent in the household) develop calcium deprivation symptoms such as cramps, headache, convulsions, etc

THERAPY

Acids—The acid must be quickly diluted with large amounts of water and neutralized with alkalis Sodium bicarbonate, sodium carbonate, milk of magnesia, chalk, soapsuds, plaster from the wall, or any other alkali at hand will serve, it should be given in relatively weak concentration but in large quantity Later, milk, egg white, starch mucilage, acacia emulsion or any bland oily substance such as liquid petrolatum or butter will be soothing Supportive drugs as indicated The value of morphine or dilaudid in decreasing pain and thus perhaps avoiding shock should not be overlooked Keep the patient warm

Oxalic acid requires certain special mention for the reason that the alkalis form salts with it that are more soluble and more toxic than the acid itself, and therefore they cannot be used Calcium and magnesium salts, however, unite with the acid to form insoluble salts wall plaster is acceptable, even though it is alkaline, and so too is lime water It should be noted that patients may experience the calcium deprivation symptoms even though they have taken too small a dose of the oxalic acid to cause the corrosive symptoms, in such cases $\frac{1}{10}$ gram (0.006 Gm) of apomorphine hydrochloride, administered hypodermically, is indicated as an emetic Action must be quick in the treatment of these cases for the poison is rapidly absorbed The intravenous administration of calcium is of course also indicated (see Lead Poisoning)

Lye and Other Alkalis—The treatment is the same as for poisoning with corrosive acids, save that here weak acids are used as antidotes, usually in the form of lemon juice or vinegar, diluted several times with water

PHENOL (CARBOLIC ACID) AND LYSOL POISONING

The symptoms are those of corrosive poisoning with additional early evidences of severe nephritis. The toxic action on the cardiovascular and central nervous systems is pronounced and almost immediately manifested, death sometimes occurs in a few minutes, often within the hour.

THERAPY

Lavage, supportive treatment, morphine or dilaudid, and the later use of demulcents, as in all corrosive poisoning, are the obviously indicated therapy. As to antidotes for phenol it seems that sodium sulfate is still the most valuable, it should be used by lavage, 4 drachms (15 Gm.) to the pint (500 cc.) of water, the washing to be continued until the phenol odor disappears. Baumann and Preusse suggested this measure many years ago because of the known conjugation of phenol with sulfuric acid arising in metabolism, the products being eliminated as comparatively harmless ethereal sulfates or sulfonates. Latterly, however, the chemistry of this reaction has come to be doubted, but the measure is a very valuable one nevertheless, perhaps due to some hindrance it offers to absorption plus the induced purgation.

Alcohol has been shown by clinical observation and the careful experiments of Macht (1915) to be of no value. The same is true of glycerin. Indeed, alcohol if given as an antidote after the poison has been taken may hasten death, despite the well known fact that a drunken individual swallowing phenol is not so seriously affected as is a normal person. These apparently contradictory facts are not understood. Gibbs (1931) recommended the administration of as large quantity of liquid petrolatum as the patient can be induced to swallow, the endeavor being to have the phenol taken up by (*i.e.*, dissolved in) this nonabsorbable oil, but Bowdler, a former phenol manufacturer, has questioned the soundness of the procedure on the basis of his experience that phenol is not readily soluble in liquid petrolatum in the presence of water. Gibb's reply was not very convincing, Goodman and Geiger (1935) have failed to substantiate his contention experimentally, but they did find olive oil to have some value in rats. Travell (1939) has recommended that olive, cottonseed, cod liver or castor oil be administered in large quantity as a first aid measure, but I have seen no case reports of the employment of such procedure.

MERCURIC CHLORIDE (BICHLORIDE) POISONING

By the time the patient is seen he has usually vomited so profusely that he is now merely retching unproductively or at most is bringing up pink mucoid material, often he is passing reddish watery stools. Abdominal pain is usually very severe unless the patient is already in shock.

THERAPY

The treatment of mercuric chloride poisoning is very unsatisfactory for the reason that practically all patients who have taken as many as 3

of the U S P tablets, containing approximately $7\frac{1}{2}$ grains (0.5 Gm) of the salt, regularly develop anuria on about the fourth day, and almost as regularly die from lesions of the kidneys, liver, or colon. I do not mean that none are ever saved, because of course they are, but the number saved is pitifully small compared with the number that die.

I shall outline briefly below the two types of therapy chiefly employed nowadays, later appending a word on "specific" antidotes and surgical measures. Morphine or dilaudid is of course indicated in any case.

Treatment Designed to Accelerate Excretion of Mercury—Since the introduction of this routine by Lambert and Patterson, in 1915, it has probably been used more often than any other, at least here in the United States.

(a) On admission, the stomach is lavaged with water, the washings being examined for mercury (which may not appear in the urine for three to twenty-four hours), and a pint of milk is introduced. Parenthetically, one may note that Sollmann *et al* (1927) found raw eggs and milk equally valuable in precipitating bichloride, but that milk will act more promptly by reason of spreading more rapidly over the stomach, egg white has no advantage over whole eggs. Lavage is repeated at hourly intervals until nausea and vomiting are allayed so that step (b) can be taken.

(b) Give every other hour by mouth 8 ounces (250 cc) of the following mixture: potassium bitartrate, 1 drachm (4 Gm), sugar, 1 drachm (4 Gm), lactose, $\frac{1}{2}$ ounce (15 Gm), lemon juice, 1 ounce (30 cc), boiled water, 16 ounces (500 cc). Administer 8 ounces (250 cc) of milk every alternate hour.

(c) Employ continuously drop rectal administration of a solution of potassium acetate, 1 drachm to the pint, to promote the secretion of urine, do not stop this enteroclysis day or night except during the irrigations.

(d) Wash out the stomach twice daily, and irrigate the colon twice daily to wash out excreted mercury.

(e) Give the patient a daily sweat in a hot pack.

(f) Two examinations of the urine for mercury, found negative on successive days, indicate that the treatment may be stopped.

Treatment Designed to Combat Shock, Dehydration and Salt Depletion—This method of treatment, introduced by Peters, Eisenman and Kydd (1933), has been quite successfully employed with more or less slight modifications by a number of observers since.

(a) Emergency treatment by gastric lavage and milk or eggs as in the older treatment above outlined, but subsequent lavaging is not routinely performed nor is the patient given fluids by mouth in the beginning.

(b) Give 1 large intravenous infusion of saline as soon as possible, and blood transfusion if evidences of shock are present or appear. If in the latter case transfusion cannot be effected at once, substitute the simultaneous intravenous injection of 10 per cent dextrose solution and the subcutaneous injection of physiologic saline solution.

(c) Give saline and dextrose injections, and blood transfusions, in quantities and intervals so regulated "as to insure the presence in the body of a large, but not excessive, supply of fluid of nearly normal composition and to maintain circulatory efficiency." Hull and Monte (1935) set the amount of fluid for the first forty-eight hours arbitrarily at 4000 to 6000 cc. Later they reduce to 3000 cc and if edema appears they go down to 1800 cc (omitting salt) merely to balance the daily fluid loss via the skin and lungs.

(d) If there is no diarrhea, rectal treatment is not given, if there is, a single small cleansing enema is administered daily.

Specific Antidotes—A great many men are earnestly engaged in this search, but so far the truly specific agent has not been found. The two following are the ones at present outstanding.

Sodium Thiosulfate—This drug has been used very much upon the theory that it effects the conversion of the poison into the harmless HgS . The results are conflicting—i.e., they are of such nature that some physicians loudly praise the drug and others loudly condemn it as worthless. The usual procedure is to administer intravenously 15 grains (1 Gm) in 10 cc aqueous solution, once or twice daily. However, in a very severe case, Marchbanks *et al* gave 10 cc every eight hours until the patient had 5 doses, and Blaisdell stated that in his hospital 10 patients had been treated without a death after it became the routine practice to give 90 grains (6 Gm) daily for three to five days. It is strange that it has not been found possible (see Melville and Bruger) to show a prolongation of life in laboratory dogs by this method.

Sodium Formaldehyde Sulfoxylate—Rosenthal introduced this drug after satisfactory animal experimentation, partially confirmed by Brown and Kolmer (1934). The drug acts by reducing the mercuric chloride to mercurous compounds, no harmful effects of the therapy have been observed in the 50 cases treated by, or known to, Rosenthal (1935), his patients recovered from the bichloride poisoning without apparent evidences of renal damage. Rabinowitch *et al* (1934) satisfactorily treated a case, Monte and Hull (1934) saw no indications of the alleged antidotal value in the 7 cases in which they used the drug, Barnes (1939) obtained remarkably rapid improvement after the use of the drug in her patient. Rosenthal's technic follows: (a) Gastric lavage with 5 per cent solution of sulfoxylate, leaving 200 cc in the stomach. (b) Immediately thereafter, intravenous administration during twenty to thirty minutes of 10 Gm in 100 to 200 cc of water. (c) In severe cases repetition of the intravenous injection six hours after completion of the first but the dose to be only 0.1 Gm per kilogram (2.2 pounds) body weight and a total of 5 Gm not to be exceeded for the adult of average weight.

Surgical Measures—Cecostomy—A number of pathologists have been impressed by the gangrenous colitis observable oftentimes at autopsy, to which Berger *et al* (1932) have given some sort of expression by advocating immediate cecostomy as soon as the patient is admitted and then the institution of constant colonic lavage. The discussion of their paper by Krumbhaar and others indicated some reticence in accepting proof of the necessity for this radical step in all cases, but the viewpoint certainly has the merit of being both interesting and new.

Decapsulation—This is the older surgical approach in anuric cases. Certainly the enthusiasm for it is hardly effusive even among the surgeons, however, Herman (1936), Pennsylvania Hospital, says, "Our small personal experience does not justify advocacy of decapsulation and yet I feel, in view of the poor results obtained by other methods, that this procedure should not be discarded without further trial." He makes the point that it adds little or nothing to the patient's burden and should probably be employed early in the anuric state.

GASOLINE, KEROSENE AND TURPENTINE POISONING

The most comprehensive report of gasoline and kerosene poisoning to date is that of Nunn and Martin (1934), who summarize the findings in 72 cases in children. Total mortality was 11 per cent, the children who finally succumbed having lived from two to eighteen hours after ingestion and aspiration of the substances. Apparently ingestion alone need not cause great anxiety, the patients manifested restlessness, incoordination, cyanosis, vomiting and loose stools, but there were no signs of pulmonary involvement, and after a succeeding period of depression, which lasted only a few hours, the children were apparently out of danger. They responded well to emptying of the stomach (Machle, 1941, stresses the importance of lavage even though forty-eight hours or more have elapsed before treatment is begun), stimulation, and catharsis. But in the patients who aspirated as well as ingested one of these petroleum products the picture was much graver owing to the rapid development of pneumonitis, as evidenced by cough and many moist râles throughout both lungs. These patients developed rapid and weak respiration and pulse, became cyanosed and restless, and developed coma and convulsions, and often died. Waring (1933) found no evidences of methemoglobin formation in the blood. No really effective treatment has been developed for these serious cases. Nunn and Martin felt that oxygen-carbon dioxide therapy was helpful in their later cases.

Turpentine poisoning appears rarely in the literature. Ross and Brown (1935) record 7 cases with 1 death in a statistical study of poisonings in children at the Toronto Hospital for Sick Children, but they do not describe the cases save to list the death as due to aspiration pneumonia. Harbeson (1936) writes "Some people exhibit a decided idiosyncrasy toward turpentine. In these 30 minims will cause vomiting and diarrhea. In larger doses there is an acute enteritis, vomiting of mucus, which is often bloody, diarrhea and passage of blood stained mucus. Large doses have a marked effect on the kidneys, causing albuminuria, hematuria, and even complete suppression." His own patient, an infant of eleven months, died in shock a few hours after the administration of 2 teaspoonfuls of spirits of turpentine by the grandmother who "thought the child had worms"—it is really a wonder that any of us is alive.

ACUTE ARSENIC POISONING

Acute arsenic poisoning is not rare, due to the fact that the arsenical pigments are much used in the arts and industries, rat and some fly and roach poisons contain arsenic, and Paris green is extensively used in rural regions as an insecticide. The symptoms usually come on an hour or more after the poison is swallowed, but may appear in a few minutes if the stomach is empty. There is pain in the mouth and esophagus, then in the stomach and entire abdomen. There is nausea and vomiting often of blood and early a profuse watery diarrhea. Paralysis of the splanchnic capillaries causes an immense quantity of fluid to escape into the connective tissues, this raises the mucosa into many large blisters and results in large pieces of

it being swept away when the fluid bursts into the lumen of the intestine. The abdomen is greatly distended and the colicky pains so severe that shock is often caused. The stools are of the rice-water type and conceivably might cause some difficulty in differentiating this condition from Asiatic cholera. There is immense thirst, scanty and albuminous urine, and finally suppression of the urine. If death does not come in a few hours to a few days, paralyses of the lower extremities are frequent, as is also fatty degeneration of the liver and kidneys.

THERAPY

The stomach should be washed out with warm water until no more arsenic can be recovered, and then warm milk or other demulcent drink may be given. A large dose of castor oil or a saline cathartic, is also indicated to flush out the poison perhaps pocketed in the upper part of the gastro-intestinal tract. If no stomach tube is available when the patient is first seen, or if its introduction is impossible or considered to be inadvisable, the emetic drugs should be resorted to, for this stomach must be thoroughly emptied.

Household mustard	1 to 2 drachms (4-8 Gm.) in water
Ipecac	1 drachm (4 Gm.) of the powder or 4 drachms (15 cc.) of the syrup in water
Copper sulfate	7½ grains (0.5 Gm.) in water
Zinc sulfate	30 grains (2 Gm.) in water
Apomorphine hydrochloride	1½ grain (0.006 Gm.) hypodermically

The mustard is the least dangerous but also the least effective. The ipecac is uncertain in action and quite depressing. Both copper and zinc sulfates cause vomiting in a very few minutes, and under the conditions obtaining here, *i. e.*, where there are no corrosions of the gastric mucosa, they are not rapidly absorbed and hence are usually not very depressing. However, if they do not cause emesis, further attempt should be made to get them out of the stomach for the reason that they are very irritant. Apomorphine is a very reliable emetic, but it is well known that the after-depression is sometimes very great.

The arsenic antidote is kept by the druggist in two bottles, one containing a solution of ferric sulfate, and the other a suspension of magnesium oxide. These are mixed when needed and the freshly precipitated ferric hydroxide is given. The dose of this precipitate is 4 ounces (120 Gm.), but it may be given 1 ounce (30 Gm.) at a time every few minutes for several doses, as it is not poisonous. Reliance is not to be placed on this antidote, for McGuigan and Atkinson (1923), confirming the earlier work of De Busscher, found that such delay in death as is obtained by its use is slight and unimportant and is probably due to the colloidal nature of the antidote and its effect upon absorption rather than to chemical neutralization of the poison. Clinical observation and impression amply confirm these experimental results, though Leschke (1934), who is able to speak authoritatively, says he thinks we are still justified in using the antidote.

The patient should of course be supported and the dehydration must be combated by all means possible.

CYANIDE POISONING

These patients are practically always in coma when the physician reaches them. There may be muscular spasms with perhaps even moderate opisthotonos. Respiration is by this time usually very shallow and irregular and the pulse of a very poor quality if perceptible at all, cyanosis is usually marked, the pupils often widely dilated. In many cases, the urinary sphincters are relaxed, there may also be froth at the mouth and the odor of cyanide on the breath. Such patients may surprisingly remain alive an hour or more after presenting this picture.

THERAPY

Artificial respiration and oxygen inhalation, gastric lavage with sodium bicarbonate solution, the usual stimulants—sometimes even 1 cc or more of hydrogen peroxide injected subcutaneously—are tried in most cases and practically always without results. In recent times, however, two "new" antidotes, methylene blue and sodium nitrite sodium thiosulfate, have begun to pile up life-saving records. There is some controversy regarding the relative merits of the two, but since cases of cyanide poisoning are relatively rarely seen it is doubtful if the real truth of the matter will emerge for a long time. The National Safety Council seems to favor the nitrite thiosulfate treatment, but on the other hand Hanzlik continues to favor methylene blue. The following treatment, described by Hanzlik and Richardson (1934) as being employed in the emergency hospitals of San Francisco though favoring the dye, amply presents both methods.

"Inject immediately 50 cc of a 1 per cent solution of methylene blue (containing 1.8 per cent of sodium sulphite) intravenously, repeat, if necessary, until a total of 200 cc is injected. Frequently, consciousness and reflexes are restored before the first 50 cc is completely injected but, if the patient lapses into unconsciousness, or manifests respiratory depression resume the methylene blue treatment. As quickly as possible, proceed with gastric lavage, using 5 per cent sodium thiosulphate. This oxidizes any unabsorbed poison. Artificial respiration, or oxygen-carbon dioxide inhalation, is given, if necessary, or as needed for the cyanosis, and caffeine or digiton hypodermically, or atropine intravenously, for circulatory and respiratory stimulation.

"The alternative procedure from the beginning is a slow and careful intravenous injection of 1 per cent sodium nitrite solution, in five divided injections, until 50 cc is injected in about one hour. If improvement is manifested but prognosis is still unfavorable, the injection may be cautiously continued, but it is to be stopped at once in case of sudden collapse. Epinephrine should be ready at hand to combat nitrite shock, if necessary. Fortify the nitrite treatment at once with the intravenous injection of 20 cc of freshly prepared 5 per cent aqueous solution of sodium thiosulphate (filtered), and, if necessary, continue the injection up to a total of 500 cc if possible. The remainder of the treatment is the same as the foregoing.

"The solutions used in these treatments can be readily sterilized by boiling for fifteen minutes."

STRYCHNINE POISONING

The presence of strychnine in some of the vermin exterminators has led to instances of accidental acute poisoning in rural regions but most of the recorded cases except in children have been suicidal or homicidal, for the dangerous nature of the drug is so well known as almost to preclude its careless handling. The patients usually say that there is a peculiar feeling at the beginning of each attack like a slow electric shock that starts above and behind the eyes and sweeps over the whole body, then the spasm begins. The usual position is that of opisthotonos. The spasms last from one half to five minutes with complete relaxation between. Consciousness is not lost and the suffering is excruciating. Between spasms there is a sensation of approaching death and the patient will plead for someone to hold him, seeming to feel that he is being ruthlessly hurled into oblivion. The usual interval between spasms is five minutes or more; most patients not surviving more than five of these full convulsions. Death is either due to asphyxia or to exhaustion. This type of poisoning must be differentiated from the following: *tetanus*, history of antecedent injury, less complete relaxation, trismus (lock jaw) and risus sardonicus earlier, much slower onset and course, much longer interval between paroxysms, absence of opisthotonos; *epilepsy*, clonic spasms, bestial sounds, absence of opisthotonos, unconsciousness, *clampsia*, complete unconsciousness during and between spasms, absence of complete opisthotonos.

THERAPY

Initiated clinically by Zerkas and McCallum in 1920 and subsequently substantiated both experimentally and clinically by numerous observers, the barbiturate treatment of strychnine poisoning has almost completely obliterated the horror with which physicians were formerly wont to view these terrible cases. Below is a condensed version of the barbiturate method presented by Kempf, McCallum and Zerkas (1933) in reporting 11 cases successfully treated.

(1) Give just enough sodium amytal or sodium pentobarbital solution intravenously to put the patient to sleep or if in convulsions to stop them. If using phenobarbital sodium, aim just to stop the convulsions even though sleep is not induced.

(2) Return of heightened reflexes, complaints about noises, marked response to slight stimuli or convulsions call for repetition of the antidote.

(3) Gastric lavage is unnecessary and inadvisable and should be done in no case unless the patient is asleep and there is adequate assistance to prevent injury or aspiration of material from the stomach. Apomorphine should not be given as it increases the latter tendency.

(4) Morphine is not indicated but quiet dark surroundings are recommended and ether may be used to control convulsions until a soluble barbiturate can be given.

(5) One should distinguish carefully between strychnine action and barbiturate effects before giving second or third barbiturate injections if in doubt wait for a mild convulsion.

(6) If barbiturates suitable for intravenous injection are not available give any barbiturate by mouth in dosage not to exceed the equivalent of 15 grains (1 Gm.) of sodium amytal for the adult i.e. in an amount not to exceed five times the ordinary hypnotic dose as stated under Insomnia.

POISONS CAUSING STUPOR OR COMA

The types of unconsciousness likely to be encountered in a private general practice, or in the receiving ward of any busy metropolitan hospital, are such as occur in the following states (1) shock following trauma, lacerations, hemorrhage, (2) electric shock, (3) sunstroke, (4) eclampsia, (5) diabetes mellitus, (6) hyperinsulinism, (7) epilepsy, (8) hemiplegia, (9) uremia, (10) central nervous system syphilis, (11) extreme cardiac decompensation, (12) extremis in any of the acute infectious diseases, (13) comatose form of pernicious malaria (rare outside the malarial zone, of course), (14) meningeal form of acute miliary tuberculosis, (15) encephalitis, (16) brain tumor, and (17) poisoning. This gruesome hand is of very diverse etiology, but all of the entities which come within the province of this book are discussed in the appropriate sections, leaving only the stupefying poisons for us to deal with in this present place. Now of course an individual taking a fatal quantity of any poison will ultimately become unconscious, but there are a few poisons which characteristically induce stupor and then coma so quickly and maintain it so firmly that unconsciousness is the chief symptom and one of the principal things to combat if life is to be saved. Overdoses of ethyl alcohol, morphine or other opiates, chloral, the barbiturates (the first taken excessively in a drinking bout, the other three with suicidal intent usually), and carbon monoxide (inhaled accidentally or purposely in a closed room or garage)—this is the list.

Alcohol—We are concerned here only with the final anesthetic stages of exceptionally severe acute alcoholism, since the hilarious and stuporous stages of an ordinary intoxication rarely come under observation for treatment as poisoning. The patient is in as deep coma as though chloral had been taken, the pupils are normal or dilated, never contracted. The skin is cold, clammy and pale, the respirations are somewhat slow and stertorous, the pulse is rapid and becomes increasingly weak, reflexes are lost, and the temperature is considerably below normal.

Morphine—The patient progresses gradually from an overpowering sleepiness into a deep coma from which it becomes finally impossible to waken him. The respirations become slower and slower and finally irregular and stertorous, and then they stop, usually the heart has been relatively little affected and continues to beat for some time after respiration has ceased. In the beginning the skin is warm and moist, but later becomes cold, clammy and cyanotic, the pupils are constricted to the so-called "pin point" dimension, but they undergo a terminal dilatation. As death approaches the sphincters relax. Convulsions are rare in adults but are sometimes seen in infants.

Chloral Hydrate.—There is deep narcosis with constricted pupils, complete muscular relaxation, very slow and shallow respiration, barely perceptible pulse, cold clammy skin, rapid fall of temperature and blood pressure.

Barbiturates—The symptoms are deep narcosis with constricted pupils, slow and shallow respiration, feeble pulse, pronounced fall in blood pressure and temperature, increased reflexes, sometimes suppression of the urine, and occasionally convulsions.

Carbon Monoxide—The patient is comatose and has a peaceful expression, though there is often twitching of the facial muscles, the temperature

is usually above normal, the skin is pale, but the lips are nearly always scarlet and there is a scarlet blush on the cheeks and sometimes over the whole body, a brownish red stippling, much resembling hemorrhagic purpura, is sometimes seen, particularly on the arms. The early symptoms are entirely due to the fact that hemoglobin has a much greater affinity for carbon monoxide than for oxygen, so that the patient is maintained in a state of partial asphyxia. If rescue is effected after only a short exposure (the degree of poisoning depending of course upon the concentration of the gas, the drafts in the room, and many other variable factors), the prognosis for recovery is good, but if profound asphyxia has persisted for very long recovery does not take place even after all of the carbon monoxide has been released and eliminated, so these cases there has been irremediable brain injury. Many of the late deaths are also due to pneumonia.

THERAPY

Gastric Lavage with Potassium Permanganate Solution—Alcohol, chloral or the barbiturates being taken by mouth, it is rational to empty the stomach thoroughly, lavage with warm water is the measure of choice because it accomplishes washing as well as emptying also for the reason that emetic drugs are very ineffective in these depressed states. If morphine was swallowed lavage is equally indicated, but careful animal study has shown that when this drug has been injected subcutaneously (as is usual in suicide cases) the small amount excreted into the stomach is very doubtfully of any importance in the final outcome, lavage is in great clinical favor, however, even in these instances. A good many years ago the substitution of potassium permanganate solution for plain water was suggested on the basis of the well known oxidizing property of the substance and such a solution has come to be very much used, accurate information regarding its effectiveness and the best concentration for routine employment is not to hand. The drug is caustic in high concentration and irritant even in fairly dilute solution, perhaps 1:5000 (8 grains [0.2 Gm.] in a quart) is about right, as Hatcher (1935) opines. Test tube studies indicate that among those poisons here under consideration, permanganate would be effective only against morphine and a few of the barbiturates (not against amytal, barbitol, phenobarbital and neonal but against alurate and dial and possibly some of the others). Subcutaneous, intramuscular or intravenous injection of the permanganate is entirely irrational.

Cathartic Measures—It is usually considered worth while in emergency services to introduce 2 ounces (60 Gm.) of magnesium sulfate in about a tumblerful of warm water before withdrawing the tube, perhaps adding $\frac{1}{2}$ ounce (15 cc.) fluidextract of cascara. If the bowels do not move in a few hours and the patient remains in coma 1 ounce (30 cc.) of castor oil is sometimes given (the tube is usually still in place in such a case) at four hour intervals until the peristaltic depression is overcome.

Diuretic Measures—In view of the excretion of barbitol and to a less extent phenobarbital, alurate and dial, in the urine, intravenous infusion as a diuretic measure has been employed in laboratory studies on dogs. So far the findings of one group of investigators completely contradict those of the other group, clinically the matter has not yet been satisfactorily tested.

Comparable studies with chloral, alcohol, and morphine have not attracted investigators because of the very slight excretion of these drugs unchanged in the urine

Stimulants (Analeptics)—A desperate effort is made to rouse the patient from stupor and to combat respiratory and circulatory depression by the use of "stimulants" injected in large doses subcutaneously or intramuscularly, caffeine sodiobenzoate, $7\frac{1}{2}$ grains (0.5 Gm), or black coffee at body temperature by rectum, strychnine sulfate, $\frac{1}{10}$ to $\frac{1}{5}$ grain (0.003–0.006 Gm), metrazol, $1\frac{1}{2}$ grains (0.1 Gm), coramine, 5 cc, ephedrine, $\frac{1}{2}$ grain (0.05 Gm), benzedrine, $\frac{1}{4}$ grain (0.015 Gm), atropine sulfate, $\frac{1}{10}$ grain (0.0015 Gm). Picrotoxin was added to the list of injectable drugs a few years ago and has won a favored position for itself, Maloney (1941) reviewing 168 cases of barbiturate poisoning treated with picrotoxin from the literature and his own experience, recommends the following method of using the drug: give intravenously 1 cc of a 1:1000 solution per minute until there is a return of the pupillary and corneal reflexes, *avoiding convulsions*. As a matter of fact, under the very variable conditions of practice it is difficult to assess the value of any of these agents for they are always used in conjunction with other measures regarding their employment in carbon monoxide poisoning. Henderson trenchantly remarks: 'The less the ambulance surgeon uses his hypodermic syringe on patients with carbon monoxide asphyxia, the better.'

Oxygen-Carbon Dioxide—In carbon monoxide poisoning the patient is likely to be breathing very poorly if at all when found. Artificial respiration must be started at once and continued until the breathing becomes spontaneous. Henderson and Haggard have conclusively shown the value of the inhalation of oxygen plus carbon dioxide. In the beginning 5 per cent of the latter was advocated, later 7 per cent, which I believe is now still looked upon by most men as the ideal concentration, though 10 per cent is advocated by some men of experience. Continuance of this gas treatment beyond one and one-half hours is useless, since by that time practically all the carbon monoxide will have been eliminated.

Latterly, reports of the use of oxygen-carbon dioxide in acute alcohol poisoning have appeared. Robinson and Selesnick (1935) found that death may be prevented and recovery accelerated by inhalation of the 90:10 mixture for a minimum time of one half hour, but the experimental studies of Newman and Card (1936) and McFarland and Barach (1936), in which both dogs and man were used did not entirely substantiate these findings. The matter certainly requires further clinical study.

Insulin-Dextrose—In alcohol cases, Goldfarb *et al* (1939) have found the intravenous injection of 50 cc of 50 per cent dextrose solution together with the subcutaneous administration of 15 units of regular insulin effected an accelerated decrease in blood alcohol. Taylor and Cross (1940) have also used this measure with apparently life-saving effectiveness in a child of about four years of age their dosage being 150 cc of 10 per cent dextrose intravenously and 10 units of insulin intramuscularly.

Miscellaneous Measures—It is of extremely great importance to keep these patients well covered and in a warm room because the loss of heat due to peripheral vascular dilatation is very great, especially in alcohol, chloral and barbiturate poisoned individuals. In carbon monoxide poisoning chilling

of the body does not occur, indeed in the beginning there is often an increase in temperature

Following the report of the resuscitation of patients poisoned with cyanide by the use of methylene blue, it was to be expected that reports of the dye's employment in carbon monoxide poisoning would follow. Several have indeed, but I believe it is now the consensus that this type of treatment is not only valueless but may even be harmful through further decreasing the oxygen carrying capacity of the blood.

Purves-Stewart and Willcox (1934) perform lumbar or cisternal puncture and drainage at intervals of twelve to twenty-four hours in serious barbiturate cases, I do not know of anyone else using this method.

The introduction of 4 per cent sodium bicarbonate solution intravenously or by rectum to combat acidosis in carbon monoxide cases is employed routinely by some men, not at all by others. Such therapy is certainly rational in the alcohol cases, for here there is an accumulation of lactic acid.

In carbon monoxide poisoning transfusion of blood in the first hour or two is tempting and is often practiced but one can only say that upon the whole the results have been disappointing.

ATROPINE, STRAMONIUM AND HYOSCYAMUS POISONING

Rather mild degrees of poisoning with members of the belladonna group are frequently seen in practice, occasionally, also, serious poisoning occurs either in an individual with an idiosyncrasy for one of these drugs or in one to whom an overdose has been given. Where the various plants having this type of action grow wild or are much used for ornamental purposes children are now and then poisoned by eating the berries or seeds or as in one of Hughes and Clark's (1939) cases through ingestion of brews of alleged anti-asthmatic properties made from them. The symptoms are very violent, but the prognosis as to life is good because of the rapid excretion of the poison. In fully developed cases the symptoms are exhibited in two phases: first, difficulty in swallowing, pain in the throat, great thirst, visual disturbances, nausea, redness of face and neck, rise in temperature, rapid pulse and excitement that goes into delirium and often into mania; second, giddiness, staggering, stupor, respiratory and circulatory collapse.

THERAPY

In Comroe's (1933) case—a patient who had swallowed $7\frac{1}{2}$ grains (0.5 Gm.) of atropine sulfate in solution one and one-half hours before being seen—gastric lavage with large quantities of sodium bicarbonate was performed in the receiving ward and 50 cc. of a saturated solution of magnesium sulfate was placed in the stomach. In the ward it was discovered that paradoxically the patient was suffering from acute pulmonary edema. After phlebotomy of 500 cc. an indwelling catheter was inserted and 400 cc. of urine obtained. When respiration became shallow, carbon dioxide and oxygen were administered. A Jutte tube was passed and 5000 cc. of water

given within forty five minutes, over half of which was vomited, continuous hypodermoclysis of saline solution was begun and cold sponges given in an attempt to reduce the fever. Maniacal outbursts were controlled with 2-grain (0.12 Gm) doses of phenobarbital. Morphine was not given because of the danger of deepening the late depression, pilocarpine was also withheld in the belief, probably correct, that myoneural junctions poisoned by atropine would not respond to it. The recovery of this patient, after ingestion of $7\frac{1}{2}$ grains of atropine, probably establishes a record.

IODINE POISONING

Accidental and suicidal poisoning with this substance is not rare. It is usually swallowed in the form of the official tincture. There are severe gastrointestinal pain, vomiting, diarrhea, hemorrhagic nephritis and depression and collapse.

THERAPY

Use the emetics (see Arsenic Poisoning) if necessary, but attempt to introduce the stomach tube as soon as possible and wash out with a starch decoction (obtained by boiling in water either laundry starch, rice or barley) until the washings no longer come away blue. The hoiled starch is preferable because it combines more actively with iodine, but lacking it in an emergency, the raw article may be used, try to get some of it down even before the passing of the tube. Sahhatani many years ago advised the employment of a 5 per cent solution of sodium thiosulfate (the plain 'hypo' bath employed by photographers is usually a 20 per cent solution) to fix the iodine as sodium iodide, I do not know to what extent this measure has ever been employed. At intervals introduce a demulcent to lessen the gastric irritation, such as eggs, milk, butter, liquid petrolatum. Treat the final depression as described under Poisons Causing Stupor.

WOOD (METHYL) ALCOHOL POISONING

This type of poisoning, that increased so much in incidence in the United States during the first years following the introduction of so-called "prohibition," markedly declined as relatively safe contraband liquor became available and now that prohibition has been officially abandoned is seen with relative rarity, the victims currently are practically exclusively among the renegade vagrants who deliberately drink denatured alcohol. This type of poisoning is characterized by a state of alcoholic inebriety, partially induced by the wood alcohol but largely by the ethyl alcohol also present in the ingested liquor, violent gastric pain and vomiting, disturbances of vision with dilated irresponsive pupils, dyspnea, cyanosis, rapid weak pulse, and a period of delirium followed by collapse. If death does not occur in

twenty four to forty-eight hours there will be partial blindness, which may clear up for a while but is again followed in many cases by total optic atrophy

THERAPY

The stomach should be washed out frequently by use of the stomach tube, though in the beginning it may be necessary to give a dose of apomorphine hydrochloride $\frac{1}{8}$ grain (0.006 Gm.) This will empty the stomach and somewhat subdue the patient in order that the tube may be introduced. Then as soon as possible give a dose of morphine sulfate by the needle, $\frac{1}{4}$ grain (0.015 Gm.), in order to lessen the patient's suffering and make cooperation more perfect, if the delirium is wild, $\frac{1}{100}$ to $\frac{1}{50}$ grain (0.0002-0.0003 Gm.) of scopolamine (hyoscyne) hydrobromide may be combined with the morphine. The lavage is to be done with 4 per cent sodium bicarbonate solution, and as soon as possible some of this solution should be introduced into the rectum, thus emptying the stomach and combating acidosis simultaneously. While Haggard and Greenberg (1939) have shown that more than 70 per cent of the ingested methyl alcohol is eliminated in the expired air, some is known to be converted into formic acid, and while it is not known that this substance causes the chief symptoms, i.e., visual disturbances, delirium, respiratory and circulatory collapse it very probably contributes much toward the acidosis that is known to be present. We have no means of destroying or hastening the elimination of this formic acid, but the acidosis we can treat. Merritt and Brown (1941) gave their patient sodium bicarbonate intravenously and believed the measure was life-saving. Keep the patient warm and support him. Before bringing the tube out of the stomach for the last time leave a large dose of saline cathartic there to flush out the bowel.

ACETANILID, ANTIPYRINE AND PHENACETIN POISONING

Acute cases of poisoning with any one or a combination of these drugs are rather infrequently seen nowadays since antipyrine, the most dangerous one of the three, is no longer used in headache nostrums, but a similar type of aniline poisoning sometimes follows the wearing of recently dyed shoes. The symptoms appear somewhat suddenly and consist of depression and confusion, dyspnea, rapid weak pulse, methemoglobin cyanosis, clammy sweat, cold extremities, and a subnormal temperature.

THERAPY

The stomach should be washed out for some time with warm water, and a dose of a saline cathartic should be left in the stomach before withdrawing the tube. Meanwhile try to get the patient warm, support him with stimulant drugs if indicated, and force fluids. Gettler and St. George (1935) say that transfusion is of tremendous value and should be given promptly. There is no specific antidote.

SALICYLATE POISONING

The general toxic effects of sodium salicylate, phenyl salicylate (salol), acetylsalicylic acid (aspirin), and methyl salicylate (oil of wintergreen) are the same, being due in each case to the salicyl radical. In most instances the symptoms develop and progress rather slowly but this is not invariable, the most characteristic of them are sweating, hyperpnea, ringing in the ears, dizziness, visual and mental disturbances, increasing stupor, and finally collapse, signs of gastro intestinal irritation are not invariably present, in some cases there are several degrees of fever. Bowen *et al* (1936) point out the ease with which this type of poisoning can be mistaken for diabetic acidosis. Mortality is very high. Fatalities have followed the taking of 300 grains (18 Gm.) of aspirin but twice this amount has been survived, 4 cc. of the oil of wintergreen has killed an infant, 6 cc. an adult.

THERAPY

It is very likely that in efforts directed toward the maintenance of renal function and the combating of dehydration lie the best hopes of saving the patient, on the basis of their animal studies, Dodd *et al* (1937) feel that if there is fever, attempts to promote the loss of heat, as by alcohol sponging, would also be of value.

Stevenson (1937) reports a very remarkable recovery, that of an infant not seen until twenty four hours after he had swallowed 15 cc. of oil of wintergreen, being then in extremis with a blood carbon dioxide combining power of 24.9 volumes per cent, albumin, blood cells, casts and 5+ acetone in the urine. The treatment in this case consisted of gastric lavage with 6 per cent sodium bicarbonate, caffeine and adrenalin injections on admission, blood transfusions, intravenous dextrose and saline, 5 per cent dextrose and solid sodium bicarbonate by mouth, 5 per cent dextrose and 5 per cent sodium bicarbonate (75 cc. of a mixture of equal parts) by rectum, digitalis, colonic irrigations, and the forcing of fluids by mouth whenever that was possible.

COCAINE POISONING

The number of fatalities from the use of cocaine is small in comparison with the large number of cases in which the drug is used, even granting that many of the fatalities are not reported, but the number of moderately severe reactions is quite large. Serious cases are of two types: (a) the patient seems suddenly to absorb the drug all at once, he gasps, clutches himself frantically, becomes very pale, falls over in a convulsion, and is dead almost before one realizes what is transpiring, (b) the events take place somewhat more slowly the patient becomes very talkative, laughs and cries unnaturally, wants to move about, there is dizziness, irregular pulse and respiration, nausea and vomiting, great abdominal pain, delirium, convulsions and finally coma and death, the entire process requires several hours. Nowadays of course most of the cases follow the application of cocaine to the mucous membranes but

occasionally they follow upon the accidental use of cocaine instead of procaine in infiltration, and rarely the use of procaine or some of the other synthetic substitutes for cocaine

THERAPY

Prevention of Absorption.—If cocaine has accidentally been injected subcutaneously, the quick application of a tourniquet above the site of injection, if this has been in one of the extremities, may be life saving, the pulse should not be completely obliterated

Stimulants—Cocaine is relatively rapidly destroyed, or at least rendered innocuous by contact with the tissues, therefore anything that will keep the patient alive for a few minutes is of value. Actually, however, the stimulant drugs have not saved many lives, though whatever is at hand should be used (see Poisons Causing Stupor for list). Herzfeld reported some years ago that the ingestion of 1 to 2 ounces (30-60 cc) of whisky or brandy ten to thirty minutes before the administration of the cocaine, was very effective in preventing unpleasant occurrences

Barbital and Phenobarbital.—Based upon the laboratory experiments of Tatum, Atkinson and Collins (1925), the use of the barbituric acid derivatives both in prophylaxis and treatment of cocaine poisoning has become quite general. Barbital, amytal or phenobarbital are usually given in ordinary or perhaps slightly larger dosage one half hour before the use of the cocaine is to begin. In cases in which signs of poisoning have already appeared these drugs are usually injected subcutaneously or intramuscularly in the form of their soluble sodium salts. Alwall (1941), in Sweden, on the basis of recent experience in 4 cases of acute poisoning, advises the use of a quick acting barbiturate such as pentothal, because after the preliminary period of great stimulation has passed it is of advantage not to have barbiturate in the blood stream to add to the succeeding period of deep cocaine depression. During the period of stimulation morphine is absolutely contraindicated because it will certainly add to the respiratory depression

METHYL CHLORIDE POISONING

Poisoning by methyl chloride had been of infrequent occurrence except industrially (Baker, 1927) until there were reported 29 cases with 13 deaths in Chicago in 1928-1929—all in Litchenette apartments in which there was discovered a leak in the multiple unit refrigerator system. A few cases have since been reported in this country (Weinstein 1937) and in England (Gorbam 1934 and Birch 1935) among workers in refrigerating and air conditioning plants. The onset of symptoms according to the careful report of Kegel *et al* (1929), is generally marked by progressive drowsiness, mental confusion, stupor, weakness, nausea, colic and vomiting; some patients experience tremor, hiccups, headache and visual disturbances. The pulse, temperature and respiration are all increased, the pupils are widely dilated, there is anuria and a blood picture suggestive of a primary anemia. Prolonged

coma is of common occurrence. Death is always preceded by severe opisthotonic convulsions accompanied by profound cyanosis. A peculiar musty, sweetish odor of the breath is a diagnostic aid.

The gas is colorless and of such faint odor as to be undetectable in even very poisonous concentration, in 2 instances in Chicago open windows in the apartment did not protect against lethal doses.

THERAPY

Kegel *et al* state that after removal of the patient from exposure, the gas is quickly eliminated, and that progressive symptoms in the more severe cases are due to continued injury from oxidation products of the gas until they are eliminated, and to degeneration of nerve cells. In the acute stage oxygen must be administered until the peculiar odor disappears even though the patient has to be restrained for the purpose. It is also considered imperatively necessary that sodium bicarbonate be got into the system in any way possible, 500 cc of Ringer's solution (sodium chloride 4.5 Gm, calcium chloride, 0.12 Gm, potassium chloride 0.21 Gm, sodium bicarbonate 0.15 Gm, distilled water 500 cc) given intravenously will further combat dehydration and acidosis. Convulsions may be allayed by potassium bromide, 1 drachm (4 Gm) in 4 ounces (120 cc) of water, given as a retention enema *but under no conditions should chloral or chloroform be given*. Stimulants as indicated. In the subsequent treatment anemia must be combated.

TEAR GAS POISONING

There is irritation of the eyes, lacrimation, and a tendency toward salivation and irritation of the throat, and slight rubefaction and mild burning of the more tender portions of the skin. Vedder (1925) said that there is no effect upon the lungs in any concentration that will be met with in the field, a statement which doubtless applies as well to the conditions under which the gas is used against mob gatherings. Goldman and Cullen (1940) make the additional statement that lethal concentrations cannot be reached in the field. However, upon exposure to somewhat more than the usual concentration it may require twenty-four hours before the eyes feel perfectly normal again and it is conceivable that enough irritation of the eyes and throat may occur in such instances to pave the way for secondary bacterial invasion with ensuing conjunctivitis and pharyngitis possibly sinusitis and otitis media.

When the contents of a tear gas gun are directly discharged against the skin or into the eyes McNally (1937) finds that prompt washing of the skin with 4 per cent sodium sulfite in equal parts of alcohol and water, and the eyes with 0.4 per cent sodium sulfite in 25 cc water and 75 cc glycerin effectively relieves distress.

The substance is not soluble in water and I therefore suppose that the only way to remove it from clothing is by mechanical flushing: e. g., slosh

cc) to be sipped well diluted, aromatic spirits of ammonia, $\frac{1}{2}$ drachm (2 cc) well diluted

Feeding with soft foods may be cautiously begun within twelve to twenty-four hours. It is usually advisable to continue the bismuth subcarbonate (without phenyl salicylate) in doses of 15 grains (1 Gm) three times daily for several days

BOTULISM

Botulism is acute poisoning caused by the toxin of *Clostridium botulinum*, an organism whose spores are widely distributed in nature being found in the soil, on fruit and vegetables, in dust, in the intestinal tract of herbivorous animals, and in the larvae of worms. The disease is caused by the ingestion of a great variety of contaminated animal and plant foods in the United States principally plant products, in Europe principally meats. Both the bacilli and the toxin are readily destroyed by boiling but the spores resist boiling for five hours and are only killed by temperatures above 230° F (110° C). Eight per cent brine, or 50 per cent sugar concentration inhibit the growth of the bacillus and prevent the formation of the toxin. In the United States and Canada, from 1899 to the middle of 1932, 193 outbreaks of botulism were reported, a total of 645 cases with 428 deaths giving a case mortality of 66.3 per cent. Between the latter date and the end of March 1942, I have seen the reports of 12 additional outbreaks in which the totals were 41 cases and 22 deaths. Most of these tragedies have been due to the ingestion of foods preserved at home without sufficient sterilization, though some have been caused by commercially canned products.

Symptoms do not usually appear until eighteen to thirty six hours have elapsed. At first there is malaise associated with constipation and subnormal temperature. Gastro intestinal symptoms are unusual and when they occur are seldom violent. Then dizziness, headache, and disturbances of vision appear scintillation, diplopia, mydriasis, blepharoptosis and loss of the light reflex. Swallowing becomes extremely difficult, the tongue coated and breath foul and the mouth excessively dry, and general muscular weakness comes on. In some cases the patient appears to be completely paralyzed but in others there are violent paroxysms induced by the attempt to swallow. The pulse is slow, then becomes rapid, breathing becomes labored and death follows from respiratory failure. Most of the victims die within three to six days, but in those who recover there are no permanent sequelae though convalescence is very slow.

THERAPY

The indications here are to empty the gastro intestinal tract, support the relieve the discomfort, and administer the antitoxin.

Emesis and Lavage —The stomach should be emptied by the use of any of the emetics listed under Arsenic Poisoning. Then a full dose of castor oil or one of the saline cathartics should be administered. This treatment is since the poison has been taken by the mouth, but what can be expected from it is sufficiently indicated in the fact that the symptoms usually

the clothes about for a long time in running water—my own idea, probably worth nothing

Queen and Stander (1941) have reported an allergic skin reaction to tear gas

FOOD POISONING

(Acute Diarrhea)

Most individuals poisoned by the ingestion of spoiled food or of contaminated water manifest the following symptoms: gastric pain, nausea and perhaps vomiting, vertigo and cold clamminess of the skin, and diarrhea often accompanied by considerable tenesmus. I have used the words "acute diarrhea" in the title because it is this symptom that causes the most discomfort to the patient after the first shock of the attack has passed.

THERAPY

The patient's stomach should be completely emptied at once. If he is much nauseated, or has already been vomiting, the introduction of several glasses of warm water into the stomach and then the stroking of the posterior pharyngeal wall with the finger, usually suffices to produce satisfactory emesis, however, one should not hesitate to use the emetic drugs (for a list see Arsenic Poisoning). As soon as the stomach is emptied a cathartic should be introduced: castor oil, 1 ounce (30 cc), or calomel, 8 grains (0.5 Gm), to be followed after six to eight hours by a saline cathartic, or magnesium sulfate, or any other saline, in full dose. McRobert (1934), in India, where extensive experience is had with food poisoning, writes that he has abandoned the early use of cathartics in favor of kaolin, 2 drachms (8 Gm) stirred in a glassful of water and sipped as frequently as possible. The patient should be absolutely at rest, take no food, and drink freely of water, hot tea or lemonade. Two hours after the cathartic has been given the administration of bismuth may be begun. 15 grains (1 Gm) of bismuth subcarbonate combined with 5 grains (0.3 Gm) of phenyl salicylate (of doubtful value) every two hours for 10 doses. The suspension may well be made as follows:

R Bismuth subcarbonate	3iv	15 0
Phenyl salicylate	3j gr xv	5 0
Glycerin	3i	30 0
Syrup of Tolu to make	3iv	120 0
Label: 2 teaspoonfuls every two hours for 10 doses.		

Colicky pain is usually controlled by 2 drachms (8 cc) of paregoric every two hours for 2 or 3 doses, occasionally it will be necessary to give a single hypodermic of $\frac{1}{4}$ grain (0.008 Gm) of morphine sulfate, or $\frac{1}{16}$ grain (0.0015 Gm) of dilaudid, combined with $\frac{1}{16}$ grain (0.0005 Gm) of atropine sulfate.

These patients are often very much depressed and need support, however, in these cases the following are possibly better to use than the true "stimulants" listed in Poisons Causing Stupor: whisky, $\frac{1}{2}$ to 1 ounce (15-30

cc) to be sipped well diluted, aromatic spirits of ammonia, $\frac{1}{2}$ drachm (2 cc) well diluted

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do not appear until eighteen to thirty six hours after the food has been ingested

Support and Stimulation—Keep the patient warm and stimulate as indicated (see Poisons Causing Stupor for a list of the stimulants) Maloney's (1939) animal studies indicate that in the very earliest stages of the poisoning picrotoxin definitely increases the severity of the symptoms, after depression has set in the drug may probably be used with safety and good effect Atropine would only add to the discomfort at any time

Relief of Discomfort—The excessive dryness in the mouth and throat can sometimes be lessened by the administration of pilocarpine nitrate, the dose of which is 1/12 grain (0.005 Gm.) hypodermically, but the advisability of employing this drug, in view of the sweat and depression that it causes, must be carefully weighed in each case

Antitoxin—It has been repeatedly shown by animal experiments that the specific antitoxin is capable of neutralizing *Cl. botulinum* toxin, but the relative infrequency of outbreaks of botulism does not warrant the distribution of this antitoxin throughout the country by commercial firms on the same scale as in the case of other therapeutic sera, a supply can always be had, however, at the Hygienic Laboratory, Washington, D. C., and at the Department of Health of the City of New York. Allen and Ecklund stated, in 1932, that Jensen and Salisbury, Inc., Kansas City, Mo., were commercial manufacturers of the product, but I have seen no recent statement on the matter. Watson (1939), of Seattle, being faced with a large outbreak of cases and having no refined antitoxin at hand, used the unpurified combined A and B botulinum antitoxin (labeled for use in animals) manufactured by the Lederle laboratories. First he gave 1000 cc. of 5 per cent dextrose in normal saline with 30 cc. of this antitoxin and 0.5 cc. of epinephrine added, allowing two hours for completion of the injection by gravity flow, later he gave doses of 1500 cc. of dextrose solution with 50 cc. of antitoxin and the epinephrine at eight hour intervals until at least 200 cc. of antitoxin had been given—thereafter 25 cc. of antitoxin was given intramuscularly at six hour intervals preceded by epinephrine. It seems to be the rather general clinical impression that by the time most cases of botulism are diagnosed it is already too late for the antitoxin to be of much value, however, Watson lost only 5 of his 16 patients which is much better than average experience, though one cannot of course draw conclusions from such small numbers.

MUSHROOM POISONING

In practically all cases of mushroom poisoning there are variable degrees of gastro intestinal disturbance nausea vomiting, gastric pain, diarrhea. In addition, depending upon the species of mushroom ingested, there may be any of the following symptoms nephritis with anuria or hemoglobinuria jaundice, excessive perspiration, salivation and lacrimation, dilatation of the pupils mental confusion, excitement, convulsions, coma and death

THERAPY

The stomach should be emptied by the use of any of the emetics (listed under Arsenic Poisoning), or with the tube. Then a full dose of castor oil or one of the saline cathartics should be administered. Keep the patient warm and stimulate as indicated. Atropine sulfate $\frac{1}{100}$ to $\frac{1}{50}$ grain (0.0006-0.0015 Gm.), will act as physiologic antidote if there is sweating, salivation and lacrimation. For the nephritis or jaundice nothing specific can be done. To quiet the excited patient, morphine sulfate $\frac{1}{2}$ grain (0.008 Gm.), or dilaudid $\frac{1}{16}$ grain (0.0013 Gm.), may be given, or any of the hypnotics or sedatives (list under Insomnia).

MILK SICKNESS

This is a very old scourge in the United States, having been known apparently to the Indians but it has never appeared anywhere else. In the early frontier days, cattle browsing in uncleared land and wild pastures were often attacked by a peculiar disease known as 'trembles' from which they died and from which birds and beasts of carrion that fed upon their carcasses died also. Man was attacked if he drank the milk or ate the flesh of infected cattle even though these products were thoroughly cooked. We now know the cause to be the ingestion by the animals of one or the other of two weeds, white snakeroot and rayless goldenrod. The symptoms in man are violent vomiting, pain and stiffness in the legs, low blood pressure and extreme weakness, obstinate constipation, swollen tongue, subnormal temperature and a characteristic odor of the body emanations. Mortality is extremely high.

Milk sickness has practically disappeared with the bringing of most of the land in the country under cultivation but Hardin stated in 1934, that she had treated more than 100 cases in the preceding sixteen years in North Carolina, and Gowen (1938) has reported 21 cases occurring in four outbreaks in Illinois in 1936 and 1937. It is a fact of no little interest that many of the apparently purposeless peregrinations of the Lincoln family during the boyhood of the future President were in reality flights from this blighting affliction. Lincoln's mother, and at least three of his close kin, died of it.

THERAPY

The studies of Bulger, Smith and Steinmeyer (1928), in animals poisoned by white snakeroot, indicated that some of the symptoms might be caused by the marked ketosis, lipemia and profound hypoglycemia which they observed. Hardin (1934) found the administration of dextrose helpful, as also gastric lavage, duodenal drainage and hypodermoclysis of normal saline. She has respect for the custom of the mountaineers to treat the attacks with brandy and honey and found that the majority of patients treated with out alcohol in some form died. Alcohol administered to the point of intoxication was the best antidote.

LEAD POISONING

The first symptoms of lead poisoning are usually abnormal fatigue accompanying irritability and sleeplessness, headache, loss of appetite and vague nausea and body pains. Constipation and increasing muscular weakness, especially of the extensors of the right hand, become marked, and then there appears tremor of the mouth and eye muscles, the latter detectable when the patient lowers the lids. Tremor of the extended fingers usually appears somewhat late, as do also actual radial paralysis and colic. During the colic—which is caused by tonic stimulation of the intestinal musculature by the direct action of the lead so that there is a contraction ring with an area of high pressure due to increased peristalsis above—the severe pains are located below the umbilicus in a scaphoid abdomen, and in contrast to appendicitis and peritonitis there is no tenderness and the suffering is relieved by pressure. The writhing of the intestines is often clearly to be felt. Frequently there is a desire to vomit and to defecate, but very little comes of this, obstinate constipation is certainly the rule, though diarrhea is on record. The patient sweats and the temperature and pulse rate are much decreased, a rise in blood pressure and blood sugar is usual but not invariable. There is also an apparent inability of the vessels to relax which accounts for the marked pallor and the slow hard pulse as well as the hypertension, this may also give rise to sudden but usually temporary attacks of blindness (the contractions can sometimes be seen in the retinal and conjunctival vessels) occasionally to contracted kidney in protracted cases to angina pectoris and gangrene of the extremities and, together with a direct poisoning of the brain cells, to encephalopathy, manifested in hallucinations babbling delirium or stupor. Whether the peripheral paralyses due to lead are of neuritic, muscular, spinal or vascular causation is not known. Sterility and miscarriage as accompaniments of the malady were recognized many years ago. Death is nowadays unusual but there may be degenerative neurologic sequelae of a most distressing sort, particularly in children, probably as a result of prolonged increase in intracranial pressure. The roentgenologic diagnosis in children is now recognized as possible, but it is my understanding that all pediatricians and roentgenologists are not at one regarding some differential points.

Pallor in this disease is not a direct expression of the anemia, for even in severe cases the red cells rarely fall below 3.5 millions and the hemoglobin below 65 per cent. With regard to stippling of the red cells, one may say (a) There is no lead poisoning entirely without stippling but there may be stippling which indicates only absorption of lead without clinical poisoning. (b) Belknap (1940) says that more than 12 stippled cells per 50 oil immersion fields (or more than 1000 per million red cells) without an associated anemia and in the face of known lead exposure, often indicates abnormal lead absorption. (c) Stippling is not entirely pathognomonic since it may also follow ingestion of silver or zinc and is promoted by potassium iodide. (d) If there is also leukocytosis, the other types of metallic poisoning, benzene poisoning, diseases of the blood forming tissues, and malaria must be ruled out. A moderate lymphocytosis is seen in some cases, perhaps a slight increase in monocytes also. The intensity of the lead line on the gums depends much upon the state of the mouth. Ruf and Belknap (1940) feel that a high lead

content of the urine means only that there has been considerable lead absorption, though they feel that findings of 0.15 to 0.2 mg per liter or over are potentially dangerous for certain cases and call for investigation, Kehoe (1941) says he has never found concentrations within the range of 0.28 to 0.36 mg except under obviously hazardous conditions of lead exposure in association with occasional cases of frank plumbism. Bellnap (1940) says that normal blood lead values may range from 0.01 to 0.06 per 100 Gm of whole blood with an occasional value as high as 0.07 and with a mean value of about 0.03 mg, but the safe level of blood lead which is compatible with a nonhazardous continuation of a given lead exposure has not as yet been adequately determined, according to this authority. Lead storage takes place principally in the calcareous portions of the bones, only secondarily in the liver and kidneys. Jaundice is due to blood disintegration and not to liver damage. A diagnostic point apparently more often resorted to abroad than in this country is the observation of a much increased coproporphyrin content in the urine. So far as absorption, storage and elimination are concerned it has been shown that the metabolism of lead and calcium are closely related but the minutiae of these processes are not yet understood. The question of delayed callus formation in lead poisoned individuals suffering fracture has been raised, and one school believes that there is injury to the calcium-secreting osteoblasts with actual bone necrosis as a possibility. The high incidence of arthritis and analogous conditions is also believed to reflect bone injury.

There is much of lead poisoning in the literature of recent centuries. Major, indeed, makes it a truly venerable disease in a delightful historical study in which he proposes one Nikander (second century, B.C.) as "poet laureate of lead colic." Not until the eighteenth century was the entity given scientific status, however, a service performed by Sir George Baker (1722-1809), who got himself denounced as a faithless son of his county for showing that Devonshire colic was due to the lead in Devonshire cider. Today, lead poisoning ranks first among the industrial diseases, and epidemics are also not of infrequent occurrence, in 1930, there were serious outbreaks in two Continental cities whose water is conveyed in lead pipes. Bizarre, indeed, are some of the ways in which we can take harmful amounts of lead into the body, but there is no space here for the list. In infants the chewing upon painted toys, the crib, etc., is probably the most frequent source.

THERAPY

After prevention of the possibility of further absorption of lead by whatever means are required in the individual case the treatment is divided into two periods: the mobilization of lead outside of the blood stream in order to bring about subsidence of acute symptoms, and the promotion of lead elimination.

Mobilization of Lead in Acute Cases—In the presence of colic or other severe acute manifestations calcium is given because as calcium is stored in the bones lead is stored also, as was shown by Aub, Hunter and their associates, in 1925. Practically instant relief is brought by the very slow intravenous administration of solutions of calcium salts, patients often going at once to sleep though some slight abdominal soreness remains. Evidently there is some antispasmodic action here also. During the period of freedom

from pain a full dose of magnesium sulfate is usually given to clean out the relaxed bowel. The calcium injection may be safely repeated if the spasm returns, as it usually does several times in the more severe cases, some men routinely repeat every three or four hours for the first twenty-four to forty-eight hours and three to four times daily for the next two to four days. Calcium gluconate, 50 cc of 5 per cent solution, is nowadays preferred to calcium chloride for the reason that if it escapes into the adjacent tissues slough will not result (to combat extravasation aspirate as much of the fluid as possible and then inject through the same needle enough sterile 0.1 per cent procaine [novocain] hydrochloride solution to distend the tissues rather markedly). The injections must be given very slowly—preferably 2 cc per minute—to avoid severe nausea and vomiting, furthermore, rapid administration may cause acute paralysis of respiration and circulation. Even at best there is usually a fall of 10 to 40 mm in the blood pressure due to peripheral vasodilatation, and the patient feels as though his entire body were on fire. During the time that injections are being given, Belknap (1935) also gives 75 grains (5 Gm) of calcium gluconate in milk three times daily after meals. The diet should be alkaline. Lacking the facilities for giving calcium intravenously, morphine and atropine must be employed, $\frac{1}{4}$ grain (0.015 Gm) and $\frac{1}{100}$ grain (0.0006 Gm) respectively, or perhaps even higher doses, the nitrites are also used, as in angina pectoris. These drugs are much inferior to calcium for relieving colic and of course they do not at all prompt lead storage in the bones. If the patient is dehydrated or there has been serious acute infection, dextrose and saline are also given intravenously.

Elimination of the Lead—After mobilization of the lead by the above means, the treatment is swung around in the opposite direction, and eliminative procedures are begun, that is to say, a regimen of calcium starvation is instituted. This is best accomplished by giving a calcium poor diet consisting of much meat, fish, eggs or cheese, and no green vegetables, a very small amount of potatoes and some milk are permissible—but very little of these. In addition deleading agents are given: (a) 20 to 30 grains (1.3–2 Gm) of ammonium chloride four to six times daily, (b) hydrochloric acid, 30 minims (2 cc) of the U.S.P. dilute if the patient can be got to take so much—administering 10 weak lemonade will help, (c) iodine, in the form of 5 to 15 grains (0.3–1 Gm) of potassium iodide, well given in milk, three times daily, often considerably increased if well borne by the stomach, (d) sodium bicarbonate 5 to 8 drachms (20–30 Gm) daily, divided into 5 or 6 portions. Leschke (1934) considers it less dangerous to use the iodide first and then, when it is felt that most of the lead has been eliminated, change to the sodium bicarbonate. His fear being of course that the promotion of too rapid streaming out of the lead will give rise to further cell injuries.

Belknap, of Milwaukee, whose industrial experience has been very large, has definite criteria for deleading, as follows: "I do not consider it advisable until all acute symptoms have subsided for a month, until the hemoglobin is 80 or above, until the red blood cell count is four million or over, and until the stipple cells have dropped to 10 or below in fifty fields (from 1,000 to 5,000 per million red blood cells) and have remained there for two or three weeks, and finally until the lead in the twenty-four hour urine is 0.15 mg. or lower. This insures that no great amount of lead is freshly liberated from the

skeleton to be superimposed on lead still freely circulating throughout the body

"For the first two or three courses of deleading, supervision is extremely close in order to note a possible return of symptoms or of the lead line with increase in stipple cells and lead in the urine. If these should reappear I am prepared to fix the lead again in a nontoxic form by high calcium intake. That the lead line does often reappear at first is to me a striking clinical proof of the efficacy of deleading. I do not delead oftener than once in four weeks, and preferably not oftener than once in six or eight weeks with the first two or three courses of deleading. In this way I avoid the unfortunate consequences of cumulating fresh lead on a preceding tide of loosened lead that has reached its peak at about two to three weeks after stimulation. For the same reason I do not prolong any course of deleading over three or four days. Though I have used them successfully in a few hospital cases I have not yet found it practical to use ammonium chloride and sodium bicarbonate or a low calcium diet in delead men who are actually at work, but it is very easy to give them their iodide drops twice a day, a safe, effective dose being 15 drops of potassium iodide or 7 drops of sodium iodide in saturated solution. Such doses may seem inadequate, but I have found from experience that they just avoid symptoms of actual iodism and that they gently stimulate lead excretion without any recurrence of serious signs or symptoms of lead intoxication.

"Using this technic, I have found that it may take from six to fifteen courses of deleading to free the individual of his most loosely combined and therefore most dangerous lead. After this, further prophylactic deleading or even the acidosis of acute infection usually fails to stimulate an increase of lead in the twenty-four hour urine above 0.15 to 0.2 mg. so that it is unlikely that there will be any recurrent toxic episodes of lead poisoning."

As most of the lead is eliminated through the bowel, the giving of saline cathartics, particularly magnesium sulfate, is considered to be especially important, senna, cascara and other drugs which may cause a more spasmodic type of movement are contraindicated, but later in the treatment mineral oil may be substituted for the salines.

The anigmal symptoms and the peripheral vascular spasmodic disturbances are treated with the xanthine diuretics as usual. In the treatment of the paralyses, months of patient massage, active movement and perhaps the application of the galvanic current are needed. Some physicians also favor the use here of large doses of strychnine sulfate, $\frac{1}{16}$ grain (0.003 Gm.) or more three times daily.

Vitamins—Theoretically, vitamin B₁ (thiamine) might be expected to be of some value in either the treatment or the prophylaxis of the chemical neuritis, but the record does not show it to have been of value in the neuritis of plumbism. Holmes *et al.* (1939) reported that the administration of 100 mg. of vitamin C (ascorbic acid) daily to each of 34 workmen exposed to factory lead hazards and actually experiencing symptoms of lead poisoning at the time resulted in general in an improvement in the blood picture and usually a disappearance of the symptoms of plumbism. Of course this is but one report and will require confirmation and a large scale controlled experiment before one can venture the opinion that perhaps vitamin C dietary therapy may in some instances replace the orthodox employment of calcium

The animal studies upon the point, performed by Pillemmer *et al* (1940), are not entirely convincing of the protective value of the vitamin. Belknap has informed me, early in 1942, that he is keeping an "open mind" upon the subject but that there is nothing in his experience to date which would lead him to believe in a specific action of vitamin C.

SNAKE BITE

The total number of deaths annually throughout the world from the bites of poisonous snakes is probably between 25,000 and 35,000, of which 20,000 to 25,000 occur in India alone. The other cases are scattered throughout all the rest of the world, few regions being without one or more dangerous families of snakes. Europe, however, is relatively free, perhaps no more than 2 or 3 fatal cases occurring there each year. The chief snakes according to their distribution are Asia, the several vipers, the daboia, the habu, the cobra, the king cobra, the krait, Africa, the vipers, the puff adder, the asp, the mamba, Oceania, brown snake, black snake, copperhead, tiger snake, death-adder, Europe, the vipers, North America, the vipers, the water moccasin, the copperhead, the rattlesnakes, the barlequin snake (southeastern United States and Central America), Central and South America, the vipers, the copperhead, the water moccasin, the rattlesnakes, the fer-de-lance, the bushmaster, the coral snake (also occurs in the West Indies), the caiaçaca, the jararacussú, the jararaca, the surucucú de patioba, and the jarará fiata.

The symptoms of poisoning vary with the different snakes. I have drawn freely upon Amaral for the following descriptions. *Cobra* local burning, edema and congestion, prostration, nausea, vomiting, salivation, cold sweats, rapid and weak pulse, rapid and later slow and weak respiration, difficulty in speech and progressive muscular paralysis, respiratory death. *King cobra* little or no local reaction, difficult and stertorous respiration, patient remains in a semiconscious state until death from respiratory paralysis. *Krait* rapid emaciation, progressive muscular weakness and other symptoms of slow intoxication, death after six or more days from respiratory paralysis. *Daboia* intense local reaction, ecchymosis and hemorrhages, nausea, vomiting and collapse with rapid weak pulse, if death is not immediate, hematuria and albuminuria, anemia, intense emaciation, and then death. *Jararaca*, *jararacussú*, *fer-de-lance*, *caiaçaca*, *habu* immediate local edema which spreads rapidly, ecchymosis, severe pain and hemorrhage at site of bite, parched throat, thirst, congestion, hemorrhages (except following the bite of the habu) into the mucous membranes and even through the skin, albuminuria, death in toxic exhaustion (habu causes respiratory paralysis and jararacussú visual impairment). *Rattlesnake* local pain, hemorrhage, ecchymosis, gangrene, rapid general symptoms (I once saw a young Negro lad vomiting and profusely sweating twenty minutes after I had seen him bitten by a large diamond back) consisting of rapid and weak pulse, nausea and vomiting, sometimes diarrhea, cold sweats, and a series of collapses until early death takes place. The pigmy rattler and the American copperhead do not seem to be among

the most poisonous snakes, also a bite by the true water moccasin (not the maligned, though vicious, common water snake) is quite rare. *Harlequin and coral snakes* no local evidences except intense pain, depression, somnolence, convulsions, death in collapse, the coral also causes salivation and lachrimation

THERAPY

Immediate Surgical Treatment—Apply a tight bandage above the knee in bites on the lower extremity, above the elbow in bites of the upper extremity, release for a few seconds at ten- or fifteen minute intervals in order to prevent gangrene below the level of the tourniquet. Traditionally it is the custom, as soon as the tourniquet has been applied, to enlarge the wound with crucial incisions 1 inch or more across and begin sucking out the venom, sucking for alternate fifteen minute periods for many hours, the tourniquet having been removed after eight hours. However, Clark (1942), discussing his experience of snake bite during many years in Central America and regions contiguous to the Canal Zone, says that such incisions are unlikely to expose the areas in which venom has been deposited since the fang is curved and the deposition of venom is not made directly beneath the fang marks, further more incisions which do happen to pass through venom droplets only increase the areas of raw surface through which rapid absorption may take place. Clark advocates simple vigorous sucking of the wound for five-minute periods off and on for an hour and then removal of the tourniquet. The application of caustics or antiseptics to the wound site is no longer advocated.

Antivenin Treatment—Obtain the antivenin at once and inject half of an ampule subcutaneously around the site and the remainder intramuscularly—in fulminating cases intravenous injection is permissible. Doses are doubled for children because the smaller the body the greater the proportionate amount of venom in the tissues. Repeat injections at one to two hour intervals unless and until symptoms are markedly diminished.

In North America—The serum is polyvalent against the venoms of rattlesnake, water moccasin and copperhead. It is marketed in 10-cc vials and is known as "Antivenin (Nearctic Crotalidae)." The problem of getting this antidote to the victim, who has probably limped into some isolated village, is of course a difficult one, however, it is believed that in time numerous stations will be established near regions badly infested by poisonous snakes, which, when reached by telephone, will send out a supply of the serum in an airplane and drop it over the place from which the call was sent. The feasibility of this plan has already been shown in the region around San Diego, California, the point of telephone call being the zoological garden in that city.

In Central America—The serum, known as "Antivenin (Bothropic)," is being extensively and effectively used in Central America since the development of the snake farm for collection of venoms at Tela, Honduras. Clark (1942) says that it is effective against the bites of all the more usual poisonous snakes of the region except the tropical rattlesnake, the hushmaster and the coral snake.

In India—Despite the fact that Calmette's serum seems to be absolutely antidotal to cobra venom, its use can hardly have made even a faint impression on the mortality record in India. The working people, scattered in

isolated villages over an enormous territory, often sleep out at night and thus fall easy victims to the wandering cobra that, seeking its meal of snakes finds the sleeping native and wantonly bites him. There is little hope that serum will ever be sufficiently well distributed that its administration will become possible to many of these unfortunates soon enough to save their lives.

In South America—We know practically nothing, of course, of the incidence of fatal snake bite in the wilds of this continent, but on the large estates and industrial workings the conditions are more favorable for treatment than in India. The working population, while scattered through the forests, particularly in the north, is more or less concentrated about the haciendas, making it easy to see the victims promptly and provide efficient care. It has been stated that the antivenins are being used successfully under these circumstances.

General Supportive Measures—Since the symptoms in seriously poisoned patients are much like those of shock, with peripheral vascular relaxation, and accompanying dehydration and alkalosis from the vomiting and diarrhea, the administration of saline intravenously is indicated. Such treatment will also possibly serve to dilute the toxin. Keeley (1937) recommends the addition of 8 minims (0.5 cc) of adrenalin to the liter of saline in the attempt to overcome the vascular dilatation. Blood transfusion and oxygen administration as indicated. The use of alcohol seems to lessen the patient's chance of recovery, popular opinion to the contrary notwithstanding.

SPIDER BITE

In the United States practically all of the authenticated cases of arachnidism have been due to the bite of *Latrodectus mactans*, commonly known as black widow, shoe-button, hourglass, and T-dot spider. To Bogen is due great credit for reawakening interest in this subject, for it is only since he made his series of reports a few years ago that the profession has become fully aware of the frequency of spider bite and the nature of the syndrome. Most of the victims have been males who were bitten on the penis or adjacent parts while sitting in an outdoor privy. The stinging pain of the bite soon subsides and there is usually little or no visible lesion, then, fifteen to thirty minutes later, pain reappears, usually at the site of the bite and spreads all over the body, reaching its maximum about an hour after the bite. There is generalized muscle spasm and very often a boardlike rigidity of the abdominal wall. The pain is agonizing but local tenderness is usually entirely absent, the patient usually sweats profusely, is restless and anxious, and may exhibit spasmodic twitching of the muscles of the extremities, priapism, localized edema and urinary retention. There may be a mild rise in temperature accompanied at times by a slow pulse, the blood and spinal fluid pressures are usually above normal.

The vast majority of the victims of this spider recover in a few days but in occasional instances paresthesias and muscular spasms and weakness persist for several weeks or even months.

THERAPY

The acute symptoms of spider bite are so severe as to necessitate immediate efforts at alleviation. Resort is practically always had to the opiates though all observers agree that these patients can tolerate very large amounts without deriving much relief from them. Hot baths are often found helpful, Blair (1934), who permitted himself to be experimentally bitten, obtained his best relief in this way, and Walsh and Hargis (1935) found baths very useful in their series of cases. Magnesium sulfate, given intravenously, was reported to be very helpful by De Asis (1934), treating 'red back' (*Latrodectus hasselti*) spider bite in the Philippines, Frawley and Ginsburg (1935) have used the drug with much satisfaction in California where our own 'black widow' had been in attendance—20 cc of 10 per cent solution, repeated as necessary to overcome spasticity and hypertension. Gilbert and Stewart (1935) reported immediate and striking relief from the intravenous administration of 10 cc of 10 per cent calcium gluconate. Mason (1938) had a similar experience, giving the injections repeatedly during the several days during which attacks of pain recurred in his patient. The use of convalescent serum has not given consistently good results nor has spinal drainage. Bogen feels and others are in agreement with him, that the stimulant drugs and alcohol should not be used, and furthermore that there is no rational indication for local treatment of the site of the bite other than the simple application of an antiseptic such as tincture of iodine.

POISONING TREATED ELSEWHERE IN THE BOOK

The places throughout the book in which the toxicology of various drugs is dealt with are too numerous to list here. The reader is requested to look in the Index for the drug in which he is interested.

BURNS

BURNS

MILD BURNS

First-degree burns or second-degree burns of only small areas are usually treated by any one or a combination of several of the following methods

Carron Oil—This substance which is a mixture in equal parts of linseed oil and lime water is soothing to burned areas like all oily and alkaline applications Gauze soaked in the mixture should be very liberally applied and held in place by bandages It is not antiseptic however and is therefore best not used on blistered areas, indeed cod liver oil (see below) will probably replace it entirely, and no great loss either

Cod Liver Oil—The oil is used in place of the above carron oil and apparently with very excellent results Indeed Steel (1935) even used it in rather extensive severe burns, but I imagine much study would be required to convince most of the justification of its employment under such conditions The oil's unpleasant odor is a disadvantage in any use of it

Picric Acid—A 1 per cent aqueous solution of picric acid is both analgesic and antiseptic and is therefore much used, its principal undesirable features are that it is inflammable and that it stains everything with which it comes in contact Small gauze compresses should be soaked in the solution and gently placed so as to cover the affected area thoroughly rather loose bandages are then employed to hold the dressing in place Any distended blisters should have been aseptically opened beforehand After two or three days the dressing may be soaked in picric acid solution to soften it and then it may be removed and replaced with a fresh one in very mild burns it is usual to leave the original dressing in place until the area is completely healed

A 5 per cent alcoholic solution may be substituted for the weaker aqueous solution, but the danger of absorption of the poisonous substance is greater in the presence of alcohol, and such a solution should certainly not be used over large areas

Aluminum Subacetate—Both Ravogli and Pusey have highly commended this substance in 2 to 5 per cent solution as both an analgesic and antiseptic of considerable value The former writes 'When the blisters are distended with serum they are opened, draining the fluid and leaving the epidermis in place to protect the denuded papillary layer Compresses of sterile gauze are applied on the burned surface and kept continually moist with the aluminum solution and the whole is bound with a piece of oiled silk so cut as to hold the dressing in place'

Ethyl Aminobenzoate (Benzocaine, Anesthesin)—Ten per cent of this substance, which is a local anesthetic, may be applied in ointment of hydroparaffin wool fat, the whole to be covered with gauze, the treatment is of doubtful value if there are blisters and danger of infection

Butesin Picrate—This substance combines the anesthetic properties of butesin with the antiseptic properties of picric acid and is an excellent

dressing for first- and mild second-degree burns. It is usually applied in the form of the N N R Butesin Picrate Ointment, which contains 1 per cent of the drug in a suitable ointment base. Before applying the dressing, all distended blisters should be aseptically drained. An unfortunate fact, repeatedly reported of late, is that many people are sensitive to this drug and develop severe dermatitis upon contact with it.

Tannic Acid—I think that most surgeons and pathologists will agree with Taylor (1936), who contends that the promiscuous use of tannic acid on mild burns is unjustified since, by needlessly "tanning" epithelial cells that might take part in repair of the denuded area, said repair may be much delayed.

SEVERE BURNS

All extensive first-degree burns, all second-degree burns unless only a very small area is involved, and all third-degree burns of whatever extent, are to be considered as serious.

GENERAL SUPPORTIVE MEASURES

Shock must be combated by the liberal use of morphine or dilaudid and the application of heat—hot water bags, blankets, the warm cradle, etc.

The late Professor Underhill maintained that blood concentration is the cause of most of the toxic symptoms of burns, but to most observers it seems more likely that anhydremia is merely one of the manifestations of a profound toxemia, the true nature of which is as yet unexplained. Still, it is recognized that if a burn involves one sixth of the body area, the loss of fluid in twenty-four hours may equal 70 per cent of the total blood volume, resulting in great blood concentration, slowed circulation, partial asphyxiation, alteration in metabolic processes, impairment of the heat-regulating mechanism with fall in temperature and suspension to a considerable degree of the vital activities. The call for fluid in large quantities is therefore imperative, and is best answered by the immediate administration of 1000 cc. of physiologic saline at a rate not to exceed 25 cc. per minute, and thereafter fluids by every available channel in the amount of 4 to 8 liters in twenty-four hours—that is until the capillaries have lost their abnormal permeability, fluids are retained and the concentration of the hemoglobin and blood chlorides approaches normal, this critical period is usually passed in twenty-four to forty-eight hours. Some observers give part of this fluid in the form of dextrose solution, which seems wise since the appearance of jaundice and depressed functional tests indicate involvement of the liver in severe cases, indeed, actual liver damage has been demonstrated at autopsy in a few instances, Belt (1939) finding the changes in the organ indistinguishable from those seen in yellow fever.

There has been occasional mention in the literature of generalized edema following such heroic introduction of fluids as above, which is thought to be due to renal depression consequent upon edema of the tubules. Permanent

renal damage does not result from burns. The edema might perhaps be more satisfactorily explained on the basis of the observations of Weimer *et al* (1936), who find serious loss of serum protein. Feeling that the store of body protein is not sufficient to restore this loss when only water, dextrose and salts are administered, they advocated the intravenous use of plasma, or of blood plasma instead of whole blood—more recently, Black (1940), Harkins (1941), Elman (1941), Tenery (1941), and Lam (1941) in his review, have stated their belief that plasma is the best available fluid for parenteral administration, superior indeed to whole blood transfusion. That the latter was itself of great value was widely recognized before plasma methods became available.

The late Dr Davidson, it seems, transfused on admission any patient with a possibly lethal burn, and repeated in less than twenty-four hours if shock developed. Seeger (1937) made it a rule to transfuse whenever there is a burn involving 20 per cent or more of the body surface, regardless of how good the patient's condition may appear to be. In children he frequently transfused if only 10 per cent of the surface is involved. Exsanguination transfusion has few sponsors any more.

Duodenal ulceration occasionally occurs as a complication of burns, but there is no way in which it may be forestalled through treatment. Sepsis also complicates some cases that have been seriously locally infected. Wilson (1936) attributes the recovery of 3 seriously toxic patients to the repeated injection of extract of the suprarenal cortex. Ivory (1940) also felt that this measure was decidedly helpful in his 3 cases and probably life saving in 1 of them—1 or 2 cc of the solution is given at intervals of one or more hours as seems indicated. One would want to see a controlled study of this method of treatment.

LOCAL TREATMENT

Before describing the methods of local treatment currently in vogue I think it should be stated that as a result of experience gained during the fortunately unsuccessful blitzkrieg against England in 1940–1941, a heated controversy developed in that country between the advocates and critics of the tannic acid treatment, the principal charge against the method being that coagulation does not control sepsis. The alternative method of treatment, which is being much advocated in England, is to control sepsis with the sulfonamides given internally and merely keep the lesions bathed in physiologic saline solution.

Surgical Measures.—Preparatory to the application of tannic acid or antiseptics, blebs should be aseptically opened and allowed to collapse and greases that may have been applied must be thoroughly removed with xylol, ether, benzene or isopropyl alcohol, heavy morphine or dilaudid dosage, or preferably general anesthesia is necessary. It has not been found that burns with chemicals require any special neutralization treatment, such as counteracting acids with alkalis for all possible damage has already been done and excess of the material can be got rid of by liberal flushing with water or saline solution. Débridement comprises the surgical removal, as completely as possible under the existing circumstances, of all burned tissue, the patient being anesthetized. It is not much practiced today because it is a sufficiently radical procedure to augment shock, it includes removal of

islands of epithelium that might otherwise be saved, the wounds are very painful, difficult to dress and liable to infection, and grafting is often necessitated that might otherwise have been avoided. Seeger says that at most debridement should be superficial and confined only to tissue which is obviously loose and destroyed, and to foreign matter in the wound.

Tannic Acid—All clothing and dressings are removed, the patient is placed under a cradle tent on sterile sheets, an electric bulb maintains warmth and dryness and the tannic acid solution (5 per cent is now universally employed occasionally raised to 10 per cent) is sprayed onto the burned area from an atomizer every fifteen minutes until a fine mahogany brown membrane is formed which usually requires from fifteen to eighteen hours. Thereafter the entire burned area, which is now insensitive, remains exposed to the warm air and the coagulum is left undisturbed until it separates—after ten days or more in deep burns, Seeger advocates drying of the crust at about four hour intervals by training a warm air hair drier on it. Also, the margins should be carefully inspected several times daily and if blebs form they must be aseptically opened and painted with a nonalcoholic antiseptic solution. Tender, elevated boggy areas should be incised, and if infection is found underneath the crust the loose portions should be removed and treatment with wet dressings (not boric acid because of danger of absorption) instituted. Seeger, accrediting the suggestion to Lee, has found that the removal of tanned membrane, should suppuration begin beneath it, is greatly facilitated by checker boarding the area with incisions during the tanning process so that 2 inch squares are formed, or the same thing may be accomplished by laying very narrow strips of adhesive across the burned area and tanning the squares between them. Large wet dressings also facilitate removal, 10 per cent sodium bicarbonate solution, or Dakin's solution if the surrounding normal skin is adequately protected by petrolatum.

Experience with tannic acid ointments or jellies (5 per cent of tannic acid in 5 per cent tragacanth jelly preserved with 1-500 salicylic acid) about the face and eyes has not been entirely satisfactory, and it is now the usual practice to use the spray here too (except upon the eyelids) since the injurious effects to the eyes which were earlier feared have not been found to occur. It is probably not advisable to use tannic acid on burns which encircle the fingers and involve both surfaces for the reason that early active motion so important here, may be interfered with.

Seeger found the least edematous disruption of tissues to occur with solutions nearest the hydrogen ion concentration of 7.4. For clinical use he prepares a solution of this acceptable concentration as follows:

Tannic acid	25.0
Pure anhydrous sodium carbonate	3.975
Water to make	500.0

Apparently this neutralization is not accompanied by any loss of tanning power. Dr Seeger informs me that experience in many cases has shown that the membrane is more pliable when this new solution is used, he also has the impression that healing occurs more rapidly beneath it. At the Cook County Hospital, according to Fantus and Dyniewicz (1937) a somewhat more elaborate formula is in use.

Potassium chloride	0 42
Calcium chloride	0 84
Salicylic acid	1 00
Sodium chloride	10 50
Tannic acid	100 00
Water to make	1000 00

This mixture must be agitated occasionally until full solution occurs and then may be filtered if desired. It is said to be bacteriostatic and to have good keeping qualities.

Tannic Acid and Silver Nitrate.—Bettman proposed this simple modification of treatment, in 1935 following the first application of tannic acid, immediately sop on a 10 per cent solution of silver nitrate, no further applications of either agent are made. The protective coagulum forms at once, thus apparently accomplishing in a few minutes what may require repeated applications during eighteen hours when tannic acid is used alone. It begins to loosen in a few days and is removed as soon as possible, unhealed areas are treated antiseptically. Results have been highly gratifying with this method and it seems that a fine advance has been made with its introduction. I have in the back of my head an unholy fear of argyria, but it is only fair to say that my friends count me quite foolish in this.

Tannic Acid Bath—Wells' (1933) variant of the treatment consists in placing the patient, immediately on admission, in a tub filled with tannic acid at a temperature regulated according to the patient's comfort. No precise percentage of tannic acid is used, just enough to give the bath a good muddy color. Water is run in, solution drained out, and tannic acid added constantly. Patients, even hysterical youngsters, are said to be completely relieved and at ease under these conditions. As the solution penetrates softens, loosens and elevates the destroyed tissue, it is painlessly removed with forceps and scissors, and the tops of blisters are wiped away with gauze. All unburned areas are scrupulously cleaned with soap and water—the cleansing continuing thus for a full three hours. Throughout this period as much fluid is given by mouth as can be taken and on removal to bed the spraying and drying as in the classical treatment is begun.

Ferric Chloride—Coan (1935) proposed the substitution of ferric chloride, in the same concentration and in aqueous solution, for tannic acid, but MacCollum (1938) pointed out the following objection to the use of this agent, it sometimes causes pain, the eschar is too thin, it stains the linen.

Paraffin, Gelatin, etc—The use of substances of this sort to protect the denuded areas is a type of primary treatment now entirely outmoded and therefore no longer to be described here with so little space at my disposal.

Continuous Bath—The continuous bath treatment is infrequently used because of the special apparatus necessary, under the constant supervision of a specially trained attendant. However, it is said to be of decided value for the first few days in extensive second- and third-degree burns of the body, especially when the patient is in coma, with a small rapid pulse, dyspnea and anuria. The continuous bath relieves pain, is sedative and improves the circulation of the skin, to some extent the absorption of toxic products is prevented. A special large tub provided with temperature regulators, large outflow pipes and rims supplied with hooks for the attachment of supporting sheets and pillows is really necessary for the proper giving of this bath.

The following rules should be observed (1) First fill the tub with hot water to warm it. (2) Regulate the temperature to 98°F (37°C) before placing the patient in the water (3) Test the temperature every few minutes, and keep it at 98°F (37°C) (4) After the temperature is adjusted, shut off the intake. Do not permit a continuous flow (5) Keep the ears dry (6) A trained attendant must not leave the room while the patient is in the tub (7) Avoid exposure on removal from the bath

Application of Antiseptic Dyes—Aldrich (1933) challenges the hypothesis that absorption of noxious materials and the abnormal concentration of the blood are the causes of severe toxemia. Instead he feels that the entire symptomatology can be accounted for on the basis of infection alone. In his investigations he found that all cultures taken from burned areas in the first twelve hours are sterile, save for the occasional occurrence of *Staphylococcus aureus* and *albus* and *Escherichia coli*, but that thereafter streptococci grow in the cultures in all severely burned patients, the concentration of the organisms increasing with the signs of increasing toxicity in the patient. He therefore treats his patients by the application of gentian violet in 1 per cent solution without preliminary cleansing of the burned area unless it is covered with oils or grease, and with the patient under a cradle maintained just warm enough for comfort. The solution is sprayed on every two hours in the beginning while the sterile eschar is rapidly forming and the wet oozing areas are becoming dry and tough, heels are then opened and the sprayings continued at four to six hour intervals during the day until healing is complete. Pain has usually ceased by the time the effect of the preliminary narcotic has worn off. Areas of softening from accumulation of secretions, liquefaction of fat or invading infection are carefully removed with forceps and the exposed surfaces sprayed. Unless actual charring has occurred, it is said that islands of epithelium spread rapidly under the scaffolding of the eschar, which is kept trimmed on the periphery as healing progresses. If grafting is to be done the eschar is removed after about three weeks by the application of warm sterile saline compresses. A patient presenting with an old burn already septic is treated in the same way without preliminary cleanup, but the eschar formed of the necrotic matter and pus is usually removed every day and the area sprayed immediately afterward.

Aldrich states that in his patients thus treated there is no great amount of prostration after the preliminary shock, that they lie quietly in no apparent pain, are cooperative in the matter of taking food and drink so that intravenous supportive measures can be dispensed with, that there is little fever and that not of the septic type, and that there are no indications of nephritis or increasing anemia and no fall in chlorides or rise in nonprotein nitrogen. Seeger (1937) says however, that in his experience gram positive cocci may occur under the gentian violet crust as well as under the tannic acid crust.

Connell *et al* (1933) used 1 per cent of the dye in a tragacanth jelly base which they place in a thick layer on 4 or 5 sheets of gauze and apply to the burned area, repeated applications being unnecessary except in severe cases. To make the 1 per cent jelly add 1 ounce (30 Gm) of tragacanth to 1000 cc of 1 per cent aqueous solution of gentian violet. Robertson (1933) apparently proceeds in about the same way as Aldrich in his cases using however a 1:800 solution of acriflavine. Narat (1937) uses a 1 per cent

aqueous solution of brilliant green, changing after a few days when pain has subsided to 1 per cent in 60 per cent alcohol and again after a few days to 1 per cent in a tragacanth jelly base

These dyes stain the bedclothes

Combination of Tannic Acid, Silver Nitrate, and Gentian Violet Treatments—Blackfield and Goldman (1939) employ the tannic acid bath during the beginning hour or more while the body and the burned areas are being cleansed with gauze soaked in green soap and water and such amount of débridement as is considered advisable is performed. The patient is then dried with sterile towels and 10 per cent silver nitrate solution is applied to the burned areas, the immediate tan which is produced is considered to save a great deal of time and quickly seal the areas before infection can take place. Thereafter, during the first few days that the patient is in the warm cradle or tent, the burned areas are treated several times daily with 1 per cent aqueous gentian violet solution. With deep burns completely encircling the hands or fingers the tannic acid or silver nitrate are not used because of the danger of their constricting action.

Sulfonamides—Pickrell (1941) reports the institution of a plan of treatment at the Johns Hopkins Hospital in which, while preparations are being made for débridement, the burned areas are sprayed with 3 per cent sulfadiazine in 8 per cent triethanolamine using an atomizer. The areas are not given prehepary cleansing in any other way, but are simply sprayed, it is said that pain is considerably allayed. After débridement, if that has been necessary, the patient is placed under a heat cradle and the sprayings continued as follows: every hour during the first day, every two hours the second day, every three hours the third day, and every four hours the fourth day. It is said that by this time a thin translucent eschar has formed and further spraying is not essential, through this eschar the progress of the healing can be followed. After about ten days, when the edges of the eschar begin to loosen and to separate from the intact epithelium beneath it, compresses of the sulfadiazine triethanolamine mixture may be applied, many times sprays of sterile mineral oil followed by normal saline compresses seem to allow the eschar to be removed in large sheets. In patients with only second degree burns Pickrell's method is to spray the areas frequently during several hours and then cover them with either sterile vaseline gauze or an ointment of 5 per cent sulfadiazine and 8 per cent triethanolamine in a stearin base, the areas are again sprayed and covered with the ointment or vaseline gauze daily until healing has taken place. Pickrell has treated 115 patients with gratifying results, a further report is promised.

In England, Robson and Wallace (1941) have used with satisfaction, especially in burns of the hands, face, scalp, feet, abdomen, buttocks, serotum and penis, a proprietary paste known as "euglamide," which contains a water-soluble sulfonamide, glycerin and kaolin. I have seen no other reports of the use of this agent.

BURNS OF THE EYE

So far as the man in general practice is concerned the objects of treatment are to remove the remnants of the chemical substance or thermal agent, which has caused or is causing the injury, and then get the patient at once into the hands of a competent ophthalmologist. If the reader objects that no such specialist is accessible in the region in which he practices I can only reply that I am sorry but that treatment subsequent to the primary cleansing is such as cannot be described here. As to the nature of the cleansing material, experience has shown that nothing is superior to water, water copiously used. Of course if the chemical is known to have been an alkali, no harm can be done by irrigating with saturated boric acid solution, while if it was an acid 3 to 5 per cent sodium bicarbonate may be employed. But water alone serves the purpose equally well, to use it quickly and freely enough are the important points.

The exception to the above is tear gas see Tear Gas Poisoning

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SULFONAMIDE TOXICITY

SULFONAMIDE TOXICITY

(Including Contraindications, Combinations and Antidotes)

NAUSEA AND VOMITING

All the drugs of this series cause nausea and vomiting to some extent. With sulfanilamide this has never been a particularly severe drawback to full employment of the drug but it early became apparent that the frequent and often severe symptoms of this sort suffered by patients taking sulfapyridine would seriously hamper the use of this drug. Sulfathiazole, however, offends much less in this respect, indeed this is probably the principal claim to superiority over sulfapyridine which this drug possesses. Witness the figures of Flippin *et al* (1941), treating 200 cases of pneumonia with each drug, sulfapyridine caused nausea in 84 per cent and vomiting in 60 per cent, sulfathiazole, nausea in 26 per cent and vomiting in 22 per cent. The newer sulfadiazine presents an even better record in the 100 cases of Flippin *et al*, nausea appeared in only 10 per cent and vomiting in only 5 per cent, other observers show similar or lower findings. Finland *et al* (1941) nausea and vomiting in 9.2 per cent of 446 cases, Dowling *et al* (1941), "slight or moderate" nausea and vomiting in 4.4 per cent of 137 cases. It seems from early reports that sulfanilylguanidine and sulfacetamide are going to have even better records than that of sulfadiazine, when used for their special purposes of gastro intestinal tract and urinary tract sterilization, respectively.

Brown *et al* (1940) reported that by suspending powdered sulfapyridine in mucilage of tragacanth the incidence of nausea and vomiting could be materially lessened. The evidence regarding the value of supplementary administration of nicotinic acid is conflicting. Whitehead and Carter (1939) stated that placing the patient in the oxygen tent for one-half hour before and after medication completely relieved nausea and vomiting in their small series of cases. Certainly all of these measures become of lessened interest now that we have the newer less toxic drugs. Even with sulfapyridine vomiting stops in from eight to twenty four hours after cessation of administration of the drug.

CYANOSIS

Cyanosis appears in a very high proportion of patients treated with sulfanilamide, in far fewer treated with sulfapyridine, and very uncommonly in sulfathiazole- or sulfadiazine treated patients. There is not agreement among investigators as to the cause of the cyanosis, some laying it entirely to methemoglobinemia, others to sulfhemoglobinemia, some to a pigment formed from the drugs, and others to diminished oxygen saturation. The oral administration of 7½ to 15 grams (0.5 to 1.0 Gm.) of methylene blue

per day is said (Wendel, 1939) to prevent cyanosis, as is also the use of nicotinic acid or the oxygen tent. But there is now general recognition that the cyanosis is harmless and can be left uncombated. Mackie (1939) has warned, however, that the taking of full doses of sulfanilamide just previous to flying will lower the aviator's "ceiling" by about 5000 feet.

NEUROPSYCHIATRIC DISTURBANCES

It is now well known that the sulfonamides sometimes cause headache, dizziness, confusion, disorientation and other behavior abnormalities, depression with lethargy and somnolence, or the opposite state of exaltation and even delirium. It is difficult to determine the absolute incidence of reactions of this nature or their occurrence with relation to the several drugs of the group, but it is my impression that sulfapyridine is in the causative role more often than sulfanilamide, sulfathiazole less often than sulfapyridine, and perhaps sulfadiazine more often than sulfathiazole. Airplane pilots are now forbidden to fly until four days after the taking of the last dose of any of these drugs, though in view of the experience of Danziger's (1938) patient, who twice had severe psychotic reactions more than four days after stopping the drug it may be that this interval of "grounding" is not long enough to cover all cases. It would certainly seem the part of wisdom for physicians to take the advice offered editorially in one of the journals recently: caution patients to stay at home and at rest while taking these drugs and during that time not to make any important decisions or sign any papers.

Visual disturbances, even to the point of practically complete blindness for a few days, peripheral neuritis and Fisher's (1939) two cases, one each of apparent ascending myelitis and encephalomyelitis, have been reported. But such reactions are extremely rare.

RENAL DISTURBANCES

The sulfonamides are acetylated, probably principally in the liver, and the acetylated together with much of the remaining free form of the drugs are excreted in the urine. In the case of sulfapyridine, sulfathiazole, and sulfadiazine the acetylated form of the drug is relatively insoluble in the urine and hence tends to appear there in crystalline form. Because they are irritating these crystals rather frequently cause microscopic hematuria and at times gross bleeding occurs. They may also collect in sufficient numbers anywhere along the urinary tract—collecting tubules, renal pelves, ureters and bladder—to cause the obstructive type of anuria. Since the relative solubilities of the acetylated forms of these three drugs are the following in increasing order, sulfapyridine, sulfathiazole, and sulfadiazine, one would

expect that the incidence of renal or ureteral disturbances with them would be of just the reverse order—i.e., that such disturbances would occur least often with sulfadiazine, more often with sulfathiazole, and most often with sulfapyridine. Garvin (1941), however, found crystals in the urine of 61.1 per cent of 54 patients treated with sulfathiazole and in only 26.6 per cent of 56 patients treated with sulfapyridine, there was no significant difference in the amount of hematuria occurring in the two groups. When enough experience is had it is highly likely that sulfadiazine is going to show the clearest record in the matter. From the standpoint of microscopic hematuria alone, Flippin *et al* (1941) find a 10 per cent incidence for sulfathiazole in 200 cases and an 11 per cent incidence for sulfapyridine in 200 cases, in another series of 100 cases each, the incidence for sulfathiazole was 9 per cent and for sulfadiazine only 4 per cent. In the latter series about 20 per cent of the sulfadiazine patients and 70 per cent of the sulfathiazole patients showed urinary crystals.

As for protection against unfortunate occurrences the best precautions are to maintain a high fluid intake and a careful watch over the urine, the latter consisting in at least daily microscopic examinations for crystals and blood, I think Arnett (1940) expresses the consensus when he says that if in addition the drug is immediately discontinued and intravenous fluids are administered with the first appearance of lumbar pain or bloody urine the dangers from renal complications will be reduced to a minimum. However the additional precaution of giving sodium bicarbonate, grain for grain with the drug, would seem to be well worth taking since Schwartz *et al* (1941) have found that it appreciably reduces the incidence and number of crystals in the urine.

Carroll *et al* (1940), and others, have found it possible to relieve these anurias by cystoscopically inserting catheters in the ureters and pelvis and lavaging with warm physiologic saline or sterile water. Smith *et al* (1940) brought about recovery in a case by resorting to bilateral pyelotomy, decapsulation and retrograde ureteral dilatation.

FEVER AND RASHES

In a small proportion of cases in which these drugs are used there occurs a secondary rise of temperature several days—usually between the fifth and ninth days, according to Long *et al* (1940)—after the temperature has been reduced to normal by the action of the drug. A rash sometimes accompanies this fever or it may appear independently of the fever. The rashes are of many forms: erysipelas like, erythematous, morbilliform, papular, nodular, urticarial, varioliform (?), scarlatiniform, petechial, purpuric, angioneurotic edemic, pemphigus foliaceus like and erythema nodosum like. Bullous eruptions and bullous stomatitis have been reported. The rash may be localized or general or the type designated "fixed." Exfoliative dermatitis has occurred and there have been some deaths. Sulfanilamide seems to cause the febrile reaction alone more often than the other drugs unless it be sulfathiazole.

This latter drug appears to be causing a good many more rashes than might have been expected in view of its relatively low toxicity in other respects. A type of reaction which seems to be peculiar to sulfathiazole consists in conjunctival and scleral injection, usually with a considerable amount of burning and a watery discharge from the affected eye. In 8 of Haviland and Long's (1940) 6 cases the eye nearest the light was disturbed either solely or at least primarily. Turkell and Wilhelm (1941) concluded that the concentration of sulfathiazole in the tears is not in itself the cause of the conjunctivitis. It appears that sulfadiazine is going to have a clearer record than sulfathiazole from the standpoint of these fever and rash reactions. Rashes following sulfanilylguanidine have been reported by both Edwards (1942) and Ringelman (1942), but this reaction like all others is of relatively rare occurrence with this drug because of its poor absorption.

The consensus is that at once upon the appearance of fever or a rash the administration of the drug should be stopped, fluids should then be pushed in order to eliminate the drug as rapidly as possible. In occasional instances dosage may then be resumed, usually upon a lower level, or one may change to another drug of the series. However, in most instances, and especially if the patient has had a severe reaction, it would seem extremely hazardous to attempt therapy again with any of the sulfonamides. Strauss and Finland (1941) found that para aminobenzoic acid was unable to overcome these drug fevers and rashes even when given in sufficient amounts to nullify the antibacterial action of the sulfonamide drug in the blood and urine. Dowling and Abernethy (1941), while agreeing that cessation of sulfonamide administration at once upon the appearance of the fever or rash is probably the wisest course, nevertheless find that it does not seem to be absolutely necessary since in 4 of their 7 cases, which occurred during the use of sulfapyridine, the temperature dropped, the rash disappeared (if it was present), and the patient recovered even though the drug had been continued on through the second bout of fever, in the other 3 cases the drug had been stopped before the rash appeared or was stopped as soon as the rash was observed. Exposure to sunlight and to artificially produced ultraviolet rays predisposes to the occurrence of rashes. Marks' (1940) experience in 2 cases indicates that the combination of x ray and these drugs may also be inadvisable.

ACIDOSIS

Since almost the very beginning of therapy with sulfanilamide, leaders in this field have been advocating the administration of 10 grains (0.6 Gm.) of sodium bicarbonate with each dose of the drug in order "to prevent acidosis." But it seems to me that the careful work of Hartmann (1939), which Carey (1940) states he has confirmed, has shown clearly that sulfanilamide actually produces a carbon dioxide deficit type of alkalosis, which would certainly provide no logical excuse for continuing this routine bicarbonate administration—indeed, the practice has caused no harm, in Hartmann's opinion, only because the doses have been small. Of course, should a real acidosis

arise, as is not infrequent in the situations in which sulfanilamide is used, it should be treated on its own merits. With the newer drugs of the series—sulfapyridine, sulfathiazole and sulfadiazine—it seems advisable to administer bicarbonate, for reasons stated under Renal Disturbances above.

HEPATIC DISTURBANCES

Sulfanilamide may cause hepatitis but the occurrence is relatively rare, it was seen by Long *et al* (1940) in only 0.6 per cent of 1000 sulfanilamide-treated cases (parenthetically, it seems to me not unfair to say that the percentage of cases in which Prentiss and Flocks (1940, found some evidence of liver damage was so amazingly high that one would want to see independent confirmation of these findings before accepting them). Hepatitis occurs even more rarely with sulfapyridine, and up to the present time (end of March 1942) I have seen no report of it in association with sulfathiazole or sulfadiazine though it is to be expected that it will occur occasionally with these drugs also. The symptoms, according to Spring and Bernstein (1940), are anorexia, epigastric distress, nausea and at times vomiting, pain and tenderness in the right upper quadrant of the abdomen, jaundice, enlarged tender liver except in mild cases, hyperbilirubinemia, urobilinuria, bilirubinuria, and decreased hepatic function. Long (1940) makes the practical point that jaundice with pale conjunctivae probably indicates that acute hemolytic anemia is developing whereas if the conjunctivae are not pale the jaundice probably results from liver damage.

Most of these cases of hepatitis fortunately clear up without sequelae if the drug administration is stopped at once and fluids are pushed, of course liberal carbohydrate administration is also indicated. But occasional cases have gone on to acute yellow atrophy and death. Many men feel that jaundice in itself contraindicates continuance of therapy with the sulfonamides, but the jaundice due to pneumonia was not so considered by Flippin *et al* (1941) in their treatment of 200 cases with sulfapyridine and 200 cases with sulfathiazole, hepatitis did not occur in any of these cases.

HEMATOPOIETIC DISTURBANCES

A number of disturbances of the formed elements of the blood occur in association with sulfonamide therapy but it should be pointed out that they are much rarer with the newer members of this series than with the original sulfanilamide. This fact, however, does not free us from the necessity of frequently and carefully scrutinizing the blood during a course with any one of these drugs. Indeed there are some indications that a routine examination of the blood one month after therapy has ceased might also be in order since

Bigg and Harvey (1941) have reported a case and cited a number of others in which serious reactions occurring as long as three weeks after cessation of therapy were felt to be reasonably attributable to that therapy.

According to Watson and Spink (1940) ordinary therapeutic doses of sulfanilamide usually cause an acceleration of hemoglobin metabolism characterized by an increase in urobilinogen in the feces and a varying increase in the reticulocyte percentage. However this may be clinicians are familiar with the occasionally occurring slowly developing *hemolytic anemia* in the course of which the patient's hemoglobin level may drop 20 per cent or more in the first ten days of treatment. According to Long *et al* (1940), who saw this happen in 3 per cent of their 1000 sulfanilamide treated cases these anemias are not to be considered alarming as they generally disappear when the drug is stopped and may be combated by the administration of 10 grains (0.6 Gm) of ferrous sulfate daily, where it is desirable to continue sulfanilamide administration, these observers feel that occasional transfusions should be given. Acute hemolytic anemia, which usually appears in the first five days of treatment, is a much more fulminating and serious affair. As previously stated Long finds that jaundice with pale conjunctivae is a valuable aid to differentiation of these cases from early hepatitis. This process seems unrelated to dosage or the concentration of the drug in the blood. The hemoglobin may fall as much as 70 per cent in twenty four hours and the erythrocyte count decrease as in Gilligan and Kapnick's (1941) case from 3,500,000 to 1,400,000 in twelve hours, there is macrocytosis, reticulocytosis, leukocytosis, an increased icterus index, urobilin in the urine, and in some cases hemoglobinemia and hemoglobinuria. Even in these cases the prognosis is good if the drug is stopped, fluids are pushed and transfusions given, but there is more than one death on record. Long *et al* think that in some instances, provided multiple transfusions are given, administration of the drug as a life saving procedure may continue until the critical period in the infectious process is passed. Tragerman and Goto (1940) suggested that the urine should be alkalinized when giving transfusions to patients having hemolytic anemia in order to prevent deposition of the obstructing pigments in the renal tubules, the measure seemed to be effective in Quick and Lord's (1941) case.

During the course of treatment with apparently any of the principal sulfonamides an acute *leukopenia* with granulocytopenia may occur, particularly in children and usually during the first ten days of therapy. In many clinics the signal for stopping the drug and pushing fluids to promote its elimination is taken to be a fall in granulocytes below 50 per cent in adults and 40 per cent in children. True cases of *agranulocytosis* in which the typical blood picture is accompanied by angina are of much rarer occurrence, they have been reported in association with sulfanilamide, sulfapyridine and sulfathiazole, but at the time of writing (late March 1942) I have seen no report of this reaction associated with sulfadiazine administration. In the experience of Long *et al* (1940) agranulocytosis is a late reaction, occurring after the fourteenth day of treatment and usually between the seventeenth and twenty fifth days, these observers say the prognosis is good if the nature of the reaction is recognized at its inception and administration of the drug is stopped at once, but there are a number of deaths on record. For full treatment see the article on Agranulocytosis.

Only a few cases of *thrombocytopenic purpura* have been reported but this is a serious reaction. The drug should of course be stopped at once and fluids pushed, for further discussion of this subject see the article on Purpura

SULFONAMIDES AND DIET

During the early days of therapy with the drugs of this group, when it was thought that cyanosis was of serious import, severe dietary restrictions were made in order to reduce the amount of sulfur absorption and thus perhaps also limit the production of sulfhemoglobinemia. Now such restrictions are definitely outmoded because cyanosis has been put in its place as an unimportant reaction and because a *really* sulfur poor dietary is a very difficult thing to provide anyway. So nowadays we feel that the patient on a sulfonamide drug may eat anything which is otherwise permissible in the disease for which he is being treated. But he should be forbidden to drink alcoholic liquors as they greatly increase the tendency toward, and the degree of, the psychotic reactions to the sulfonamides.

SULFONAMIDES AND OTHER DRUGS

I know of no evidence indicating that any other drug which may seem necessary cannot be safely given at the same time that a sulfonamide is being administered. Hewer (1938) warned that perhaps pentothal should not be used for intravenous anesthesia since it contains sulfur and there are many men who are afraid to administer magnesium sulfate as a cathartic for the same reason, to me it seems that this position has no more warrant here than it has in the case of dietary restrictions (see above).

SULFONAMIDE CONTRAINDICATIONS

Long (1940) says that if an individual has previously had a severe *sulfonamide reaction* and the use of one of these drugs is subsequently indicated one should first give a small test dose of $2\frac{1}{2}$ to 5 grains (0.15 to 0.3 Gm.) and then observe the patient for twelve hours thereafter, if nothing has happened, treatment may be cautiously begun and pursued with especial watchfulness. Since these drugs are very imperfectly excreted if there is *impaired kidney function* one should use them with the greatest of caution in such a situation, Allen (1940) suggests that under these circumstances the excessive acetylation of the drugs may increase their toxicity. The opinion has been

several times expressed by leaders in the sulfonamide studies that previously existing *jaundice* or *liver damage* is not a contraindication to sulfonamide therapy especially if the hepatic damage is a result of infection for which these drugs are indicated. Cleveland's (1939) report is an evidence of what daring will sometimes accomplish in such cases: his patient had a severe postoperative cholangitis, marked liver damage and jaundice and yet full sulfonamide dosage was employed and apparently saved her life. Schwartz and Flippin (1941) say that the presence of *anemia* or *leukopenia* before therapy is commenced does not contraindicate the use of sulfathiazole (the only drug upon which they were reporting). In the presence of severe *cardiac arrhythmias* and especially of *congestive heart failure* these drugs should be used with utmost caution: one had perhaps best be cautious in the use of these drugs in *coronary disease* also for I have heard of instances in which their use increased the sub-sternal distress. The sulfonamides have been administered at all stages of *pregnancy* apparently without harm still one should be a bit on guard and perhaps expectant of some case reports that are perhaps still being accumulated. A straw in the wind may be the paper of Heckel (1941) who felt that the severe anemia in the infant of 1 of 13 women whom he had given sulfanilamide during pregnancy suggested fetal injury by the drug. It is the same with regard to the *nursing mother*. I have seen no report as yet (late March 1942) of injury to the infant from sulfonamide-containing milk but perhaps an occasional case will appear in the near future.

SULFONAMIDE ANTIDOTES

There are none. Push fluids to hasten elimination, employ such special measures as are indicated in the various types of toxic reaction and remain hopeful.

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